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MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY, PART 3,--ETC(U)
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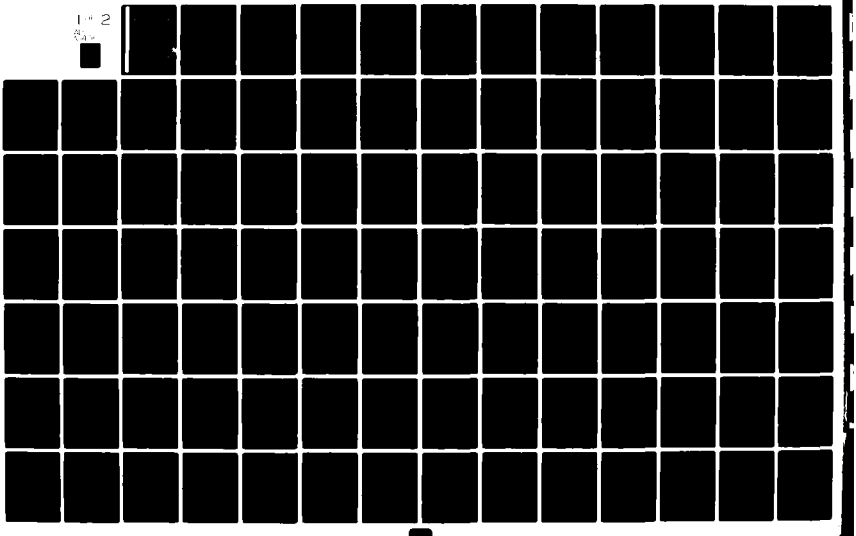

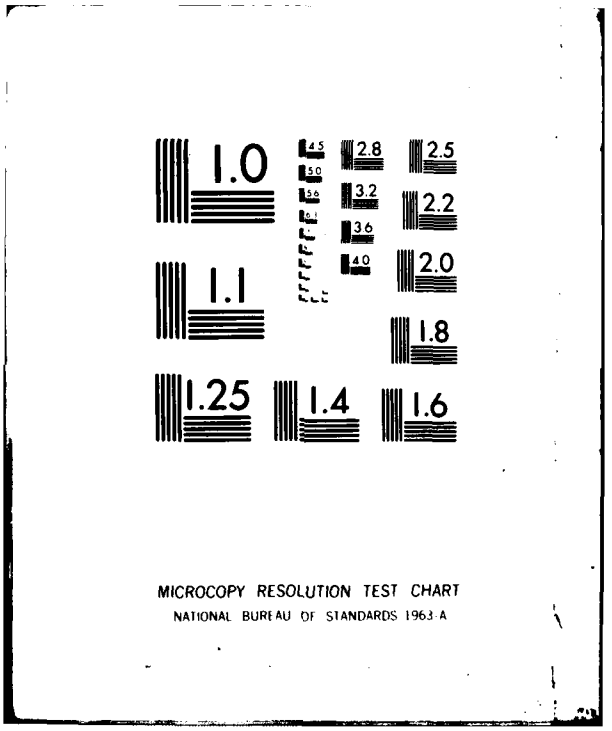
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LSI TR-477-4

MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY

IMPACT OF FUTURE CHANGES REPORT (U)

by
R. J. Davenport and J. P. Glennon

March, 1981

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract DAMD17-81-C-1013

Life Systems, Inc.
Cleveland, OH 44122

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Impacts of Toxicology Changes, Mammalian Toxicology Testing, Toxicology Regulatory Changes, Toxicology Advances, Mammalian Toxicology, Mammalian, Toxicology, Toxic Substances Control Act, Clean Air Act, Federal Water Pollution Control Act, Safe Drinking Water Act, Resource Conservation and Recovery Act, Federal Insecticide, Fungicide, and Rodenticide Act.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Toxicology technology advances and regulatory changes for the period 1981 to 1990 were identified and analyzed for impacts. It is anticipated that major increases in nearly all toxicology testing resources will be required as a result of future regulatory actions. These actions will primarily be based on current statutes and will occur despite the forecast that no major legislation will be enacted. Toxicology testing may also increase to allow

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production of an improved human health hazard data base for better decision-making on regulations changes. Federal spending constraints will force regulatory agencies to use their present authority to require "private" sector toxicology testing to satisfy this increased need. Other nonregulatory requirements for increased testing to fill existing data gaps were also identified.

Significant shortages are forecast to continue for the following trained professionals: veterinary pathologists, inhalation toxicologists, pharmacokineticists and toxicokineticists, neurotoxicologists and biostatisticians. Teams of toxicology support personnel will be developed to reduce the workload on these professionals, resulting in increased diversity of toxicology technical staffs. Increased diversity will also be reflected in the animals and testing procedures used.

Conclusions and recommendations regarding the impact of these changes are provided and early warning "flags" of forecasted changes are identified.

Reports provided under the subject Contract include three major final reports and 12 supporting documents.

EXECUTIVE SUMMARY:

AN EVALUATION OF REGULATORY AND TECHNOLOGICAL CHANGES

THAT MAY IMPACT TOXICOLOGICAL TESTING REQUIREMENTS

Background

The 1980's could be said to be the decade for performance of the regulatory goals formulated during the 1970's. The Clean Air Act, for example, which was amended in 1977, requires that the primary air quality standards must be met by the end of 1982. The Clean Water Act, first passed in 1948, did not contain major, explicit, national goals until the 1972 amendment which requires compliance by mid-1983. Sixty-five families of toxic pollutants were added to the Clean Water Act in 1978, but their standards will not have been fully promulgated until 1987.

". . .The chemical industry hasn't begun to feel the effects of a mature and fully functional regulatory system (Toxic Substances Control Act)", said Gerald Laubach, President of Pfizer, recently.

While the Safe Drinking Water Act regulates bacteria, turbidity, certain inorganic chemicals, pesticides, and radionuclides, standards for ten more organic chemicals and ten more inorganic chemicals, viruses, and protozoa will only be established in 1981. And finally, the Solid Waste Act, which covers almost 500 million metric tons annually of municipal and industrial wastes, only put into effect in late-1980 its "cradle to grave" manifest system. Standards have yet to be promulgated.

If one were to couple the immense backlog of toxicological testing represented by this pending implementation of the nation's major environmental laws with the current worldwide capability of only 500 reliable, long-term bioassay test programs per year, it is clear that demand and supply for toxicological testing are on a collision course. The collision, in fact, has already occurred; its impact will inevitably worsen before it can begin to improve, because it is realiably estimated that there will be a need for at least 1000 annual bioassay programs during the next decade.

With the cost of a long-term, two-species test already ranging from $500,000 to $750,000, an economic crunch of serious proportions will be worsened by escalating labor costs due to the worldwide competition for qualified professionals (not to mention the impact of continuing high-level inflation).

The problem confronting the U.S. Army is a serious one. A decision must be made as to how the Army will meet its toxicological testing requirements, who will do it, and how much it will cost. Affecting this decision will be the possible impacts of future regulatory and technological changes. The purpose of this task was to develop the most reliable possible forecast of the decade ahead as it pertains to toxicological testing.

Approach

A team of experts representing the prinicipal disciplines comprising toxicological testing was assembled by Life Systems, Inc. (LSI) to forecast likely technological testing changes. Their opinions were obtained through position papers prepared by each expert and through an exchange of ideas during a "brain-storming" meeting.

Eight persons were on the team: four were university-affiliated, two were from the National Academy of Sciences, one was from NIOSH, and one was from the Albert Einstein Medical Center.

Since too large a team would have had to be assembled to forecast regulatory changes, a single, extremely experienced individual performed this task through personal interviews and a literature review.

The forecasts of technological and regulatory changes were then reviewed and their impact was projected by Drs. Davenport and Glennon of LSI, who also prepared the final report for Task 10.

The Task team worked within a framework of some 20 assumptions or guidelines embracing task management, regulatory and technological changes, and the Army's need for toxicological testing. One of the assumptions was that 10 years is the maximum horizon for making credible projections.

Impact of Regulatory Changes

Factors Affecting Regulatory Changes

Regulatory changes are primarily affected by political pressures, public involvement, industry pressures, technology changes, economics, and international factors. Although political pressures under the Reagan Administration are expected to slow down or even roll back a number of regulations, the focus will be primarily toward "end-point" compliance regulations mandated by Congress and not toward regulations that will decrease toxicological testing.

Public interest is likely to stay high during the coming decade, and public-comment periods are built in to nearly all rule-making processes. Although "public" comments can actually often be comments from industry, the new generation of people who grew up with an environmental education will resist major changes in existing legislation and health standards.

Industry's influence on regulatory changes will increase in the next decade, favored in part by the climate toward reducing over-regulation of industry. Industry can also be expected to promote the concept that more toxicological data are needed in order to postpone compliance with a regulation believed to be unjustified.

Technological changes in toxicological testing, by introducing cheaper, faster tests, can strongly affect the pace of regulatory changes. They are also likely, paradoxically enough, to increase the short-term volume of toxicological testing because of the need for data corroborating the validity of new technology.

Economics has had and will continue to exert a major influence on regulatory change. Risk-benefit analyses will become even more a part of the process and, in the words of the outgoing EPA Assistant Administrator for Toxic Substances, ". . . the close calls will be decided in favor of economics. . ."

International factors impacting on regulatory change will pull both ways. Foreign manufacturers who export chemicals to the U.S. will have to meet TSCA requirements. Over a longer period, toxicological data of foreign countries will increasingly meet U.S. regulatory standards, thus eliminating duplication and the amount of toxicological testing the U.S. will have to perform.

Impact of Regulatory Changes on Toxicological Testing

The overwhelming cumulative impact of the forecasted regulatory changes will be to increase the amount of toxicological testing worldwide. (The only way this might prove to be untrue is if there should be major downgrading or repeal of present legistlation, a highly unlikely prospect.)

Even though no major new legislation involving toxicological testing is foreseen for the next decade, major increases will nevertheless be required in all toxicological resources (personnel, equipment, facilities, and money). Disregarding inflation, costs will rise because more compounds will be tested, more testing will be required per compound, salary costs will increase due to heavy competition, and more data will be needed even in support of proposed relaxations in certain regulations. Specific forecasts of the impacts due to regulatory changes for the next decade are as follows:

- Demand for toxicological testing resources will approximately double
- Lack of trained personnel will be the most serious impact
- All toxicological testing programs worldwide, both governmental and industrial, will have to deal with these impacts
- Specialized tests not in current protocols will become commonplace after mid-decade
- Long-term animal studies will be a continuing requirement
- Toxicological testing will probably be subject to increased emphasis on quality assurance and control (e.g., GLP)
- More human exposure assessments will be required
- An improving toxicological data base will increasingly satisfy requirements of certain regulatory agencies
- Technological innovation will be reduced because of the competition of heavier testing requirements

Impact of Technological Changes

Factors Affecting Technological/Change

Knowledge gaps, economics, politcal and industrial pressures, and regulatory influences all can affect technological change. Knowledge gaps increase the cost and complexity of tests and data interpretation. By building the toxicological data base and eliminating these gaps, test results can be extrapolated from animals to humans with greater accuracy.

Economics exerts a heavy influence on technological change by causing pressure for simpler, less costly test protocols and procedures, by improving quality control so as to avoid having to repeat tests, by changing protocols so as to get more data per test, and by improving statistical treatment so as to get more value from data.

Political pressures can reflect the public's concerns and thereby increase the need for more, and more thorough, testing. Industrial pressures tend to promote extensive testing so as to delay or prevent substances from being declared hazardous. Industry also is motivated to press for simpler, less costly tests to prove materials are not hazardous.

Regulatory influences affect technological change by formalizing protocols and procedures, and by providing inertia which tends to maintain well established, costly tests currently in use.

Impact of Technological Changes on Toxicological Testing

Little, if any, significant change is expected in the basic toxicological tests during the next 10 years. Three tests, in particular, are so well established that changes in them are very unlikely:

- Single-exposure acute toxicity test (LD_{50})
- Subchronic (90-day) test
- Chronic (2-year, two-species) test (recently reduced to 1 year for carcinogenicity testing)

Significant gaps exist in the current technology data base. Elimination of data gaps would greatly facilitate interspecies correlations, and extrapolations of data from animal studies to determine acceptable human exposure levels. This would also enable replacing many costly animal testing with short-term in vitro tests. Knowledge of the nature of the reactions occurring would simplify projecting toxic effects, based on the structure of individual chemicals and groups of chemicals. Fewer tests would have to be performed since conclusions could be reached on the basis of tests using a few chemicals from each group.

Mathematical models, while initially requiring more data because of their greater sophistication, will eventually result in a substantial reduction in toxicological testing. This will not occur during the next decade, however. Math modeling also increases the need for computer equipment and specialized computer and information/data personnel.

Short-term screening tests are being developed, primarily to be used to prioritize the testing of potentially hazardous substances. They will help assure that limited testing resources are spent where they will do the most good. They may also eventually replace some animal tests.

Tier approaches -- particularly structure-activity relationships (SAR) -- are helping agencies that have urgent needs to rapidly develop rationale for decision making.

Definitive tests are being developed either to meet recently recognized effects or to improve the extrapolation of data from animals to humans.

Many changes in testing procedures are underway or planned. Their general impact is to increase the need for toxicological testing resources, either initially or permanently. Testing facilities similarly are experiencing many changes, most of which require more initial resources. Human studies are also undergoing change, but of a nature which has little impact on the utilization of resources. Likewise, quality assurance changes are not expected to impact heavily on testing technology.

Changes in data interpretation, primarily the increasing use of computer equipment, are affecting technology and initially adding to the cost of toxicological testing. Eventually, but primarily beyond the term of this forecast, these changes will be a major force in bringing down the cost of toxicological testing.

As in the case of regulatory changes, the overwhelming combined impact of these and other forecasted technological changes will be to increase the toxicological resources required during the next decade. Specific forecasts of specific impacts are as follows:

- More toxicologists, pharmacokinetists, toxicokinetists, neurotoxicologists, and paraprofessionals will be required
- More analytical chemists, veterinarians, QA personnel, programmers, modelers, information specialists, and librarians will be needed
- Greater specialization will occur, both as a result of the chronic shortage of toxicologically trained professionals and of the inherent effectiveness of the use of specialists
- Toxicological testing facilities will be more diverse, reflecting the needs of specialists as well as the technological changes that will occur in toxicological testing
- Universities may have to take up some of the testing load; this will require that they conform to GLP and adapt to the confidentiality requirements of industrial clients
- If universities cannot provide enough trained professionals, toxicological testing facilities will have to train or retrain personnel to meet their own needs

- Numbers of animals required will approximately double, with a proportinate increase in holding facilities
- Improved waste water treatment and solid waste incineration equipment will be required
- The very high cost of waste disposal may result in some form of joint use of such equipment by facilities located close to each other
- More and larger computer equipment will be required
- Core analytical facilities will be developed at testing labs, but outside services will increasingly used for other specialized analytical support (e.g., GC/MS)
- New facilities will be laid out flexibly to accomodate future changes, by such means as modularized offices and labs, movable walls, etc.

FOREWORD

A Mammalian Toxicology Testing Problem Definition Study was conducted for the U.S. Army Medical Research and Development Command, Ft. Detrick, Frederick, MD, under Contract DAMD17-81-C-1013. The Study's Prinicipal Investigator was Dr. R. A. Wynveen. COL Alfred M. Allen, Toxicology Project Officer, Letterman Army Institute of Research, was the Contracting Officer's Technical Representative. Mr. Michael F. Travis was the Contracting Officer's Representative. Ms. Jean Smith was the Contracting Officer.

Reports for this Contract, DAMD17-81-C-1013, consist of three major final reports and twelve supporting documents. The Contract title, MAMMALIAN TOXICOLOGY TESTING: PROBLEM DEFINITION STUDY, is the main title for all the reports. Individual reports are subtitled and referenced with Life Systems, Inc. (LSI) report numbers as detailed below.

Report Subtitle	Life Systems, Inc. Report Number
Final Reports--	
Part 1. Comparative Analysis Report	LSI-TR-477-2
Part 2. Facility Installation Report	LSI-TR-477-3
Part 3. Impact of Future Changes Report	LSI-TR-477-4
Supporting Documents--	
Technology Changes Impact on Testing Requirements	LSI-TR-477-14
Quality Assurance Plan	LSI-TR-477-17A
Capability Modules	LSI-TR-477-19B
Technical Plan	LSI-TR-477-20A
Equipment Plan	LSI-TR-477-21A
Personnel Plan	LSI-TR-477-23A
Inhalation Chambers and Supporting Equipment Survey	LSI-TR-477-26A
Equipment List for Modules	LSI-TR-477-28B
AMTR Protocol/Pricing Report	LSI-TR-477-29A
Global Army Toxicology Requirements	LSI-TR-477-31A
Comparison Toxicology Test Costs	LSI-TR-477-36A
Annual Testing Capacity	LSI-TR-477-38A

This is the Impact of Future Changes Report.

This Contract supported technical efforts by Life Systems' personnel, various supporting organizations and Consultants.

This report was prepared by the Interdisciplinary Consulting and Information Research (ICAIR) Systems Division, Life Systems, Inc. The effort was completed under the overall direction of Dr. Richard A. Wynveen, Principal Investigator. Dr. Ronald J. Davenport was the Project Manager for this task. Dr. John P. Glennon served as the Task Manager. The final report, prepared and assembled by Dr. Ronald J. Davenport and Dr. John P. Glennon, is based on input from a Team of ICAIR Consultants (see Section 2.0). Editorial assistance was provided by Mr. David G. Jenkins and Mr. Donald Culver.

Citations of organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organization.

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LIST OF ACRONYMS

BAT	Best Available Treatment (water pollutants)
CIIT	Chemical Industry Institute of Toxicology
CPSC	Consumer Product Safety Commission
DOA	Department of Agriculture
DOC	Department of Commerce
DOE	Department of Energy
DOI	Department of Interior
DOL	Department of Labor
DOT	Department of Transportion
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FSQS	Food Safety and Quality Services Administration
FWPCA	Federal Water Pollution Control Act
GLP	Good Laboratory Practices
HHS	Department of Health and Human Services
ICAIR	Interdisciplinary Consulting and Information Research Division of Life Systems, Inc.
IRLG	Interagency Regulatory Liaison Group
ITC	Interagency Testing Committee
LD	Lethal Dose
LSI	Life Systems, Inc.
MCL	Maximum Permissible Contaminant Level (drinking water)
NAAQS	National Ambient Air Quality Standards
NAS	National Academy of Sciences
NCI	National Cancer Institute
NDI	National Death Index
NESHAPS	National Emissions Standards for Hazardous Air Pollutants
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NSSPS	New Stationary Source Performance Standards (air pollutants)
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OPTS	Office of Pesticides and Toxic Substances, EPA
OSHA	Occupational Safety and Health Administration
POTW	Publicly Owned Treatment Works (water pollutants)
PSD	Prevention of Significant Deterioration (air pollutants)
PWS	Public Water System Supervision Program
RCRA	Resource Conservation and Recovery Act
R&D	Research and Development
RDT&E	Research, Development, Testing and Evalution
RPAR	Rebuttable Presumption Against Registration (pesticides)
SDWA	Safe Drinking Water Act
SIP	State Implementation Plan (air pollutants)
TSCA	Toxic Substances Control Act
UIC	Underground Injection Control Program (drinking water)
USPHS	United States Public Health Service
WHO	World Health Organization

INTRODUCTION

The purpose of this document is to summarize forecasts that have been made related to potential regulatory and technology changes that may impact the resource requirements for future toxicology testing. The ten-year period between 1981 and 1990 is the focal point for these projections; however, where it was possible with some degree of certainty to make projections beyond that period, longer-term projections have been included. A ten-year time span was selected to provide information beyond the three to five year program and budgetary guidance normally available to Government decision-makers. The ten-year forecasts can then be used to select near-term resource commitments that are likely to have long-term (ten years or more) payoffs. Forecasts beyond ten years were not specifically attempted because of the increasing uncertainty associated with such projections. Long-term forecasting would require the application of data gathering and modeling techniques that were beyond the scope of this effort.

This report was prepared as a specific subtask of a larger effort to evaluate many aspects of the U.S. Army's present and projected toxicology testing program. It is believed that changes in that program are, and will continue to be, shaped by four major influences:

1. External toxicology testing requirements. Federal, state and/or local regulations to generate specific human health (and environmental) hazard information.

2. Internal toxicology testing requirements. The Army needs to understand the human health (and environmental) hazards associated with items in its inventory and to develop new or replacement items that have minimum hazards.

3. Changes in available toxicology testing technology. Techniques that are: less expensive, faster, more predictive of human effects than present techniques, predictive of human effects that were previously untestable (e.g., due to absence of an appropriate animal model) etc.

4. Changes in available resources. Specific fluctuations in funding, facilities and/or personnel to support the Army's toxicology testing program.

This report deals only with items 1 and 3 in a comprehensive manner. Forecasts of internal Army testing requirements and resource constraints (items 2 and 4, respectively) are beyond the scope of this subtask. Some aspects of these other important influences are being dealt with under other subtasks of this overall effort. For example, the capability modules for the potential mammalian toxicology facility were selected and designed based upon future Army-specific toxicology testing requirements. Still other aspects will have to be dealt with by the Army as part of its routine program management. For example, changes in available resources will have to be evaluated on a periodic basis and toxicology testing program priorities established accordingly.

In this context, many of the conclusions and recommendations made in this report have general applicability to other organizations (e.g., private industry) that face regulatory and/or internal toxicology testing requirements. Thus, the report represents a stop-off point from which to develop specific forecasts focused to the Army's unique requirements.

Changes in toxicology technology are very difficult to project with a high degree of accuracy because of the speed by which that technology is changing and because of the broad scope of present toxicology basic research. Unanticipated breakthroughs can occur on many fronts. Yet, in order to comply with the needs for advanced planning, a practical approach to projecting technology changes was undertaken. This involved assembling a team of experts from diverse subdisciplines within the realm of toxicology testing. From the distinct perspective of their subdisciplines, each expert provided his projections of technology changes, first individually and then later as part of a group discussion.

Forecasts of regulatory change also have a significant amount of uncertainty due to the controlling influences of changing political environments (e.g., new Administrations), uncertain directions in the economy and unanticipated technology advancements. The team approach was considered impractical for this portion of the effort. This is because a large number of regulatory agency representatives, industry representatives, members from public interest groups and political figures would have to be assembled on the team to obtain a representative cross-section of regulatory projections. Therefore, a single individual, with extensive experience in the regulatory arena, performed information gathering efforts (e.g., personal interviews, review of reference literature) and summarized the projected regulatory changes.

For the purpose of this study, only significant changes were considered. Significant changes are those that would result in a measurable change in either the type or amount of resources required after the change has occurred. Changes, rather than trends, are emphasized because of the limited ability to make projections of any sort. Changes are considered to be a significant alteration that can be described qualitatively but not quantitatively. The use of the word "trend" would imply the ability to make quantitative measurements of the degree of change.

Finally, this report documents the projected impact on toxicology testing resources resulting from predicted changes. It is this information that planners of toxicology testing facilities require. Also, planners and managers can benefit from the identification of some indicator or "flag" that would signal that the predicted change is imminent. Where such flags could be identified, they provide the toxicology program manager a mechanism for updating these forecasts.

APPROACH

The strategy used in performing the changes impact evaluation is described below. The organization of the effort is described and the team members participating in the effort are identified.

Table 1 illustrates that the changes impact evaluation consisted of three Tasks. The first was the forecasting of potential regulatory changes that may impact toxicology testing standards and/or data required for compliance with toxicology testing regulations. The second Task was the forecasting of significant changes in toxicology testing technology. The third Task was the definition of the impacts that the projected regulatory and technology changes would have on the needs and approaches to toxicology testing.

The approach used for each task is summarized in Table 2. Information on possible regulatory changes (Task 1) was obtained from a variety of organizations involved in either establishing regulations or attempting to influence the direction taken by regulatory agencies. The information obtained from these organizations consisted partly of documents summarizing their projections for changes, or efforts to influence regulatory changes. Information was also provided verbally through meetings and telephone discussions. The organizations contacted in this effort are listed in Table 3. Mr. Alan Cywin, assisted by a group of technical and administrative personnel from within the ICAIR Systems Division of Life Systems, Inc. (LSI), assembled and organized this information to prepare the Impact of Regulatory Changes Section of the report.

A different approach was utilized to make forecasts of possible toxicology technology changes (Task 2). For this effort, experts in animal husbandry, behavioral effects, biochemistry (structure-activity relationships), biostatistics, epidemiology, general (acute/subchronic/chronic) toxicology, genetics, inhalation toxicology, mutagenicity, neurotoxicology and oncology (Table 4) provided written summaries of their projections. This technique was selected to minimize bias that might otherwise result from the input of only one or two experts. These experts then participated in a Review Meeting on January 21, 1981 to discuss and identify concensus opinions regarding the probability and impact of the forecasted technology changes.

The coordination of all inputs (Task 3) from Tasks 1 and 2 and the preparation of the Final Report was performed by Drs. Ronald J. Davenport and John P. Glennon of the ICAIR Systems Division of LSI.

The overall plan for the technical and administrative activities, and the schedule provided for this effort, are summarized in Figure 1.

The forecasts of regulatory and technology changes presented in this report should not be considered infallible predictions of future events. The forecasts represent concensus opinions and judgements from the participants in this effort. The accuracy of the forecasts will remain unknown for several years. The credibility of the forecasts probably could have been increased by performing a larger and more scientific sampling and statistical analysis of opinions and judgements. This, however, would not necessarily improve the accuracy of the forecasts. Thus, the forecasts presented in this report are subject to debate and revision as unanticipated changes (or absence of changes) takes place during future years.

It should also be noted that all forecasts dealing with regulatory or technology changes were included in this report regardless of the present known or suspected relevance to the Army's toxicology testing program. That would require input from the Army that was not available at the time this effort was performed.

TABLE 1 ORGANIZATION OF THE IMPACT OF CHANGES EVALUATION

Task	Description
1	Forecast potential regulatory agency changes that may impact toxicology testing requirements
2	Forecast potential technology changes that may impact toxicology testing requirements
3	Define the combined impact of projected regulatory and technology changes on the resource requirements for future toxicology testing

TABLE 2 APPROACH USED IN THE TOXICOLOGY TESTING CHANGES EVALUATION

Task	Approach
1	Information obtained from variety of organizations involved in predicting, influencing and formulating toxicology regulations: • Prepared documents • Verbal communications
2	Information obtained from recognized experts in subdisciplines involved in toxicology testing technologies: • Position papers prepared by experts (referencing relevant technical literature) • Verbal exchange of ideas at Technology Changes Review Meeting
3	Information from Tasks 1 and 2 reviewed and summarized, and the impact of the forecasted changes upon toxicology testing resources defined

TABLE 3 SOURCES OF REGULATORY CHANGES INFORMATION

	Organization	Point of Contact
1.	AFL-CIO National Office	Ms. Semanario
2.	Chemical Industry Institute of Toxicology	Dr. Gralla
3.	Chemical Manufacturers Association	Mr. Strickland
4.	Conservation Foundation	Mr. Erwin
5.	Council on Environmental Quality	Mr. Milvy
6.	Environmental Action Foundation	Mr. Wentworth
7.	Environmental Defense Fund	Dr. Highland
8.	Environmental Protection Agency	Provided by Mr. Cywin[a,b]
9.	Food and Drug Administration	Provided by Mr. Gittes[a] and Mr. Cywin[a,b]
10.	Interagency Regulatory Liaison Group	Mr. Hein
11.	Izaak Walton League of America	Ms. Leonard
12.	National Academy of Sciences	Dr. Tardiff[a]
13.	National Agricultural Chemical Association	Drs. Hollis, McCollister, Barnett, Spurrier, Levinskas
14.	National Institute of Environmental Health Sciences	Dr. Shapiro
15.	National Resources Defense Council	Ms. Bird
16.	National Toxicology Program	Dr. Huff, Mr. Hayseman
17.	Occupational Health and Safety Administration	Provided by Mr. Cywin[a,b]
18.	Office of Management and Budget	Messrs. Clark, Strasser Isinger
19.	Office of Technology Assessment	Ms. Gelband
20.	Rachel Carson Council	Ms. Briggs
21.	Ralph Nader, Center for Study of Responsive Law	-
22.	Senate Committee on Human Resources	Messrs. Grossman, Scrabitt
23.	Sierra Club	Ms. Kochick
24.	University of Pennsylvania, Wharton School	Ms. Franklin
25.	U.S. Regulatory Council	Ms. Jacobs, Smalley

(a) ICAIR Consultant
(b) Specific sources of information cited in text and listed in Reference Section.

TABLE 4 SOURCES OF TECHNOLOGY CHANGES INFORMATION

Subdisciplines	Experts	Affiliation	Years of Exper.(a)	Other Information
1. Biostatistics	Dr. John Van Ryzin	Columbia University	23	66 Books and Publications; Assoc. Ed. of Annals of Statistics
2. a. Epidemiology b. Biostatistics	Dr. Kenneth Rothman	Harvard University	14	45 journal publications; Editorial Boards of New England Journal of Medicine, Am. Journal of Epidemiology
3. a. Genetics b. Mutagenesis c. Genetic Toxicology	Dr. William Lee	Louisiana State U.	27	48 Publications; Member Editorial Board Environ. Mutagenesis
4. a. Inhalation Tox. b. Industrial Tox. c. Animal Husbandry	Mr. William Wagner	National Institute of Occupational Safety and Health (NIOSH)	30	33 Publications; Supervisory Pharmacologist, U.S. Public Health Service, NIOSH
5. a. Neurotoxicology b. Behavioral Effects	Dr. Peter Spencer	Albert Einstein Medical Center	12	57 Publications; Director of Institute of Neurotoxicology at Albert Einstein Medical Center
6. a. Oncology/ Biochemistry b. Structure-Activity Relationships	Dr. Benjamin Van Duuren	New York University Medical Center	29	Assoc. Director of Institute of Environmental Medicine

(a) Years since BA/BS

continued-

Table 4 - continued

Subdisciplines	Experts	Affiliation	Years of Exper.(a)	Other Information
7. Toxicology, General	a. Dr. Gordon Newell	a. National Academy of Sciences (NAS)	a. 31	a. 66 Publications; Assoc. Execut. Director of Board on Toxicology and Environmental Health Hazards, NAS
	b. Dr. Robert Tardiff	b. NAS	b. 16	b. 44 Publications; Executive Director of Board on Toxicology and Environmental Health Hazards, NAS

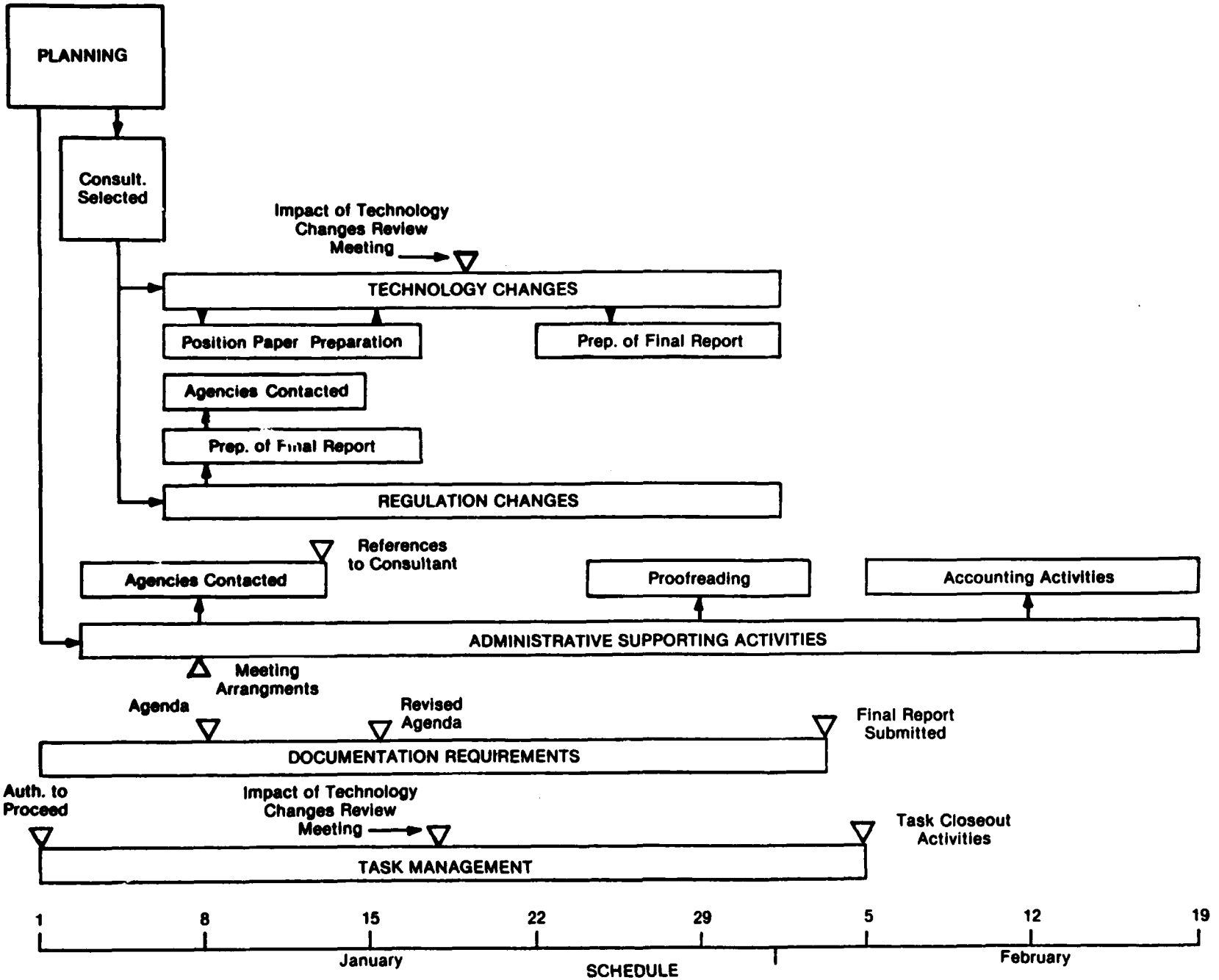

FIGURE 1 SCHEDULE

Further, this would have introduced an unnecessary constraint on the forecasting process that could inhibit free thought and expression by the participants. Finally, some forecasts of questionable present-day relevance to the Army's program may become important factors in the future.

ASSUMPTIONS

Assumptions have been made to facilitate progress and to focus the attention of the Team Members upon those areas most germane to the needs of planners and managers of toxicology testing facilities. These assumptions are listed below.

Management Assumptions

The following assumptions were used in the management of this effort.

1. No projection of future events can be totally accurate. However, knowledge of likely changes is available within the community of (1) organizations dealing with regulations, environmental quality, industrial and business needs, and (2) leading experts within the area of toxicology testing itself. It has therefore been assumed that projections made using these sources will provide information that is valuable to planners and managers of toxicology testing facilities.

2. A consensus among different sources of information is not necessary to develop a forecast. Therefore, information may be obtained to develop multiple scenarios for future changes based on the divergent views from conflicting information sources.

3. A ten-year period is the longest time period for which projections can be made with any degree of credibility.

4. There are significant indicators or "flags" that will signal that a forecasted change is imminent, increase the probability of the change, or provide a better indication of the timeframe for the actual change. It is further assumed that there are planners and managers who will be alert to the flags and their significance once flags are identified.

5. The information obtained from forecasts of the sort provided here will assist the Army to anticipate and satisfy its regulatory toxicology testing needs more efficiently and effectively than would be possible otherwise.

Assumptions Related to Regulatory Changes

1. Regulatory changes will be slower to occur than non-regulatory (technology) changes.

2. State and local regulatory agencies will be dominated by Federal laws in terms of the requirements for toxicology testing (data base development). This is contrasted to the significant role States

presently play, and will most likely continue to play, with regard to standard-setting and enforcement.

3. There will continue to be increased concern on the part of organized labor concerning workplace health conditions.

4. As the percentage of the U.S. population over 60 years of age increases, there will be a proportionately increased concern and support for regulations dealing with effects that impact older persons. Of particular relevance to this evaluation are those toxic effects which require a long latent period (e.g., carcinogenic effects).

5. The political influences represented by the new Reagan Administration will remain relatively consistent throughout the next decade. This assumes, for example, that concern for the economy will continue to influence most Government decision-making and that major failures or successes by the Reagan Administration (or successive Administrations) will not upset this emphasis.

6. No major catastrophic events (war, natural disaster or deep economic depression, etc.) will occur during the next decade to totally revise Governmental and societal priorities. This also assumes that the Army will not request an exemption from any toxicology testing regulatory requirements on the basis of national security or other reasons of paramount interest to the United States as permitted by Executive Order 12088.

Assumptions Related to Technology Changes

1. Projections should be focused on significant changes that may take place during the next decade. A significant change is assumed to be one that will modify the time, cost, type or amount of equipment, type or number of personnel, design of overall facilities, etc., required to perform toxicology testing. Technology changes which do not have these types of impact have much less importance to decision-makers who are attempting to forecast future resource requirements. For example, if a toxicology screening method gains wide acceptance as a decision-making tool in a comprehensive testing protocol, this may not represent a "significant" change. It would only be significant if new, unique facilities or personnel were required to perform the test, or if the results could be used to replace certain longer-term animal tests.

2. The amount and rate of technology change, is generally proportional to the amount of "basic research" funding provided. As budgetary constraints are levied on basic research programs (primarily university-based), a reduction in the pace of technology advancements will be observed.

3. The amount and rate of technology change during the next decade will be inversely proportional to the number of senior-level professionals that leave basic research positions (e.g., university positions) to assume toxicology performance testing and management positions in

Government and industry. This assumes that the inspiration for technology advancements will come from the senior experts in the toxicology field. Loss of these individuals to Government or industry (to perform or manage state-of-the-art toxicology studies) will reduce the amount or rate of technology change. This also assumes that the junior-level professionals remaining in basic research positions do not possess the expertise or experience to inspire technology advancements to the same degree as the senior-level professionals.

The converse of this relationship is also assumed. If there is an influx of senior-level professionals into basic research positions, the amount and rate of technology advancement will increase. The relative salary structure between these competing career areas is assumed to be the principal indicator or "flag" for this relationship.

4. Significant technology changes will not occur as sudden, major breakthroughs. Rather, technology advancements will occur in incremental steps as new ideas are formulated, tested, refined and validated. Thus, there will be a number of indicators or "flags" in the toxicology community to signal when a technology change will gain acceptance and be used as the basis for regulatory agency decision-making.

Assumptions Related to the Army's Needs for Toxicology Testing

1. The Army's toxicology testing requirements (and overall human health hazard assessment program) come from three primary sources:

   a. Items already in the Army inventory (i.e. items already in use for which there are known or suspected human health hazards).

   b. Items in Research, Development, Testing and Evaluation (RDT&E) (i.e., known or suspected human health hazards associated with items currently under development).

   c. Items that are projected for future development (i.e., known or suspected health hazards associated with items that are currently in the concept stage of development).

2. The Army's toxicology testing program is structured to meet regulatory requirements. An example here is the Army's irradiated food program.

   The following is a list of federal regulatory organizations that are relevant to the Army's toxicology research program:

   a. Food and Drug Administration (FDA)
   b. Environmental Protection Agency (EPA)
   c. Occupational Safety and Health Administration (OSHA)
   d. Consumer Product Safety Commission (CPSC)
   e. Department of Agriculture (USDA)
   f. Department of Commerce (DOC)
   g. Department of Energy (DOE)

h. Department of Interior (DOI)
i. Department of Transportation (DOT)

Added to this list are a number of State and local regulatory organizations which have supremacy over certain environmental health hazards, and certain international requirements that may influence peace-time Army operations in foreign countries. The EPA, OSHA and FDA promulgate most of the regulations that generate specific toxicology testing requirements relevant to the Army.

Their relevance here first stems from the fact that the Army maintains a large industrial base and an extensive human services (medical) program to support its national defense missions. The production, distribution, testing and use (during training) of military weapons systems and hardware generates human health concerns in both the occupational and general environments. The Army must evaluate human health hazards under the "cradle-to-grave" concept to ensure protection of human health not only during the production and use of items, but also during and following ultimate disposal when items become obsolete or unservicable. It is emphasized that the Army had established regulations in this area prior to enactment of the Toxic Substance Control Act (TSCA) and the Resource Conservation and Recovery Act (RCRA) which established this concept of responsibility for the entire industrial community.

The second major area directly impacted by regulatory requirements is the Army's comprehensive health program. This includes conventional health services for military members and their dependents, and, more importantly, a requirement to protect the health of the soldier under adverse environmental conditions (extreme climatic regions, tropical disease areas, chemical warfare environments, etc.). Toxicology testing here may be in support of new drugs and vaccines, food additives (for field rations), and medical devices/materiel. These require adherence to the regulatory requirements promulgated by the FDA and EPA. The latter is particularly relevant for pesticides used in preventive medicine programs.

It is emphasized that the Army's toxicology testing program to meet regulatory requirements is limited in scope. The Army will be responsible for performing this type of testing only for Army-unique chemicals or for common use items of very high Army priority (relative to the civil sector). Within the context of this report, when the Army performs testing in direct response to regulatory requirements it is part of the "public" sector, i.e., a non-regulatory Government organization.

3. The Army's toxicology testing program is also structured to meet nonregulatory requirements. These are internal goals and objectives for the Army to:

   a. Prevent decrements in soldier performance by eliminating or reducing human health hazards.

b. Reduce compensation payments.
c. Reduce litigations and settlements.
d. Improve the selection of materiel alternatives by identifying the least hazardous materiels/components for Army items.

These nonregulatory requirements are internal Army incentives for self regulation where the Army recognizes performance or economic advantages for supporting human health hazard assessments in the absence of, or in advance of, specific regulatory requirements to do so.

4. The Army's general toxicology testing requirements mirror those of the U.S. society. The Army is both the producer and consumer of its products. It maintains a comprehensive conventional health care system for its members and eligible dependents. It is responsible for occupational health, both in the traditional industrial setting, and in the testing and training activities somewhat unique to the military. It is responsible for environmental discharges from its industrial and municipal facilities. These discharges may have an adverse impact on the surrounding civilian population. It maintains a large number of "self-sufficient" communities. These are both permanent and temporary communities. In addition, some of the unique activities associated with its national defense mission dictate that the Army must deal with materials that are more hazardous to human health than an "average" civilian industry or community. Therefore, the Army's toxicology testing program has no boundaries. It must be comprehensive and it must take advantage of the latest advancements in the state-of-the-art for evaluating human health hazards.

IMPACT OF REGULATORY CHANGES

The toxicological testing necessary to satisfy appropriate Federal, State and local regulatory agency requirements is interrelated. This is because the regulatory agencies share the common goal of obtaining information for the protection of human health, and they therefore use the same technology base. The Federal Government's role in promulgating requirements to develop toxicological data began with the Federal Food, Drug and Cosmetic Act (FFDCA) of 1938. In the 1960's and 1970's, the Federal Government assumed a much larger responsibility, in both the environmental and occupational health area, through several landmark legislative mandates. Responsibilities for regulatory efforts which had been administered by each State jurisdiction were shifted to the Federal Government and are now largely under the authority of the EPA and OSHA under the Department of Labor (DOL).

Through this centralization, the nation has developed a more uniform regulatory approach for evaluating and controlling toxic chemicals, under similar conditions across State boundaries. Many of the features of the various statutes (especially environmental laws) still provide for State implementation of the Federal regulations and standards. Federal research programs (including toxicology) have grown in support of the Federal regulation and standard setting process.

Federal, State and local compliance regulations are the primary product of the health assessment process in response to legislative mandates. As legally enforceable limitations, the Federal regulations constitute the "last word" on specific toxic chemicals. In recent years, the public has supported a rapid proliferation of such regulations. The speed with which these regulations have been promulgated (and amended) has caused concern and confusion among those affected by them. Thus, there is also an "over-regulation" backlash being generated by industries and other groups that are immediately affected.

A generalized and somewhat idealized sequence of events in the regulatory process for human health hazard assessments is shown in Figure 2. Congress must first pass a Public Law in response to a perceived problem. This will stimulate technology developments to permit implementation of the Law. Technology developments could be through regulatory agency supported research, specifically recognized by Congress in the law and/or the application of technology already developed for related purposes. This in turn leads to toxicology testing, data evaluation and interpretation and decision-making, all resulting in an enforceable compliance requirement intended to protect public health from the problem area(s) perceived by Congress. Feedback loops exist at all locations in this sequence making this an iterative rather than a once-through process. Requirements to recycle through portions of this sequence come from many sources. For example, Congress may amend the goals and objective of the Law; technology developments may identify inadequacies in the existing data base or prior decision-making; toxicology results may be inconclusive, requiring repeated or more definitive testing; or affected organizations (e.g., industry) may successfully challenge the compliance requirements through litigation.

It is important to recognize that the regulatory agencies promulgate specific regulations at many points in this sequence to implement the Public Law. The enforceable compliance regulations, at the end of the process, are the most visible and generally have the greatest cost impact on those affected. A clear distinction must be made between these "end-point" regulations and those which dictate the type, amount and performance responsibilities for toxicology testing earlier in the sequence. As will be discussed later, changes in these "end-point" regulations do not necessarily result in similar types of changes in the regulations dealing with toxicology testing. Indeed, many changes that roll-back or remand "end-point" regulations actually result in regulatory agency actions to require more toxicology testing.

One of the most challenging aspects of the process for toxic chemicals is that the regulatory agencies are required to make both qualitative and quantitative determinations regarding a chemical's human health hazard. The Public Laws are too poorly written with respect to scientific direction and appreciation of the available technology to permit confidence during the decision-making process. Thus, decision-making that is based on information from a still developing technology sets up an atmosphere that invites challenge and requires reevaluation leading to change.

There are a number of indicators or "flags" that will (1) signal an approaching regulatory change, (2) increase the probability that the change will occur or (3) provide specific information on the impact the change will have when/if it comes about. Table 5 provides a listing of such flags at the Federal govern-

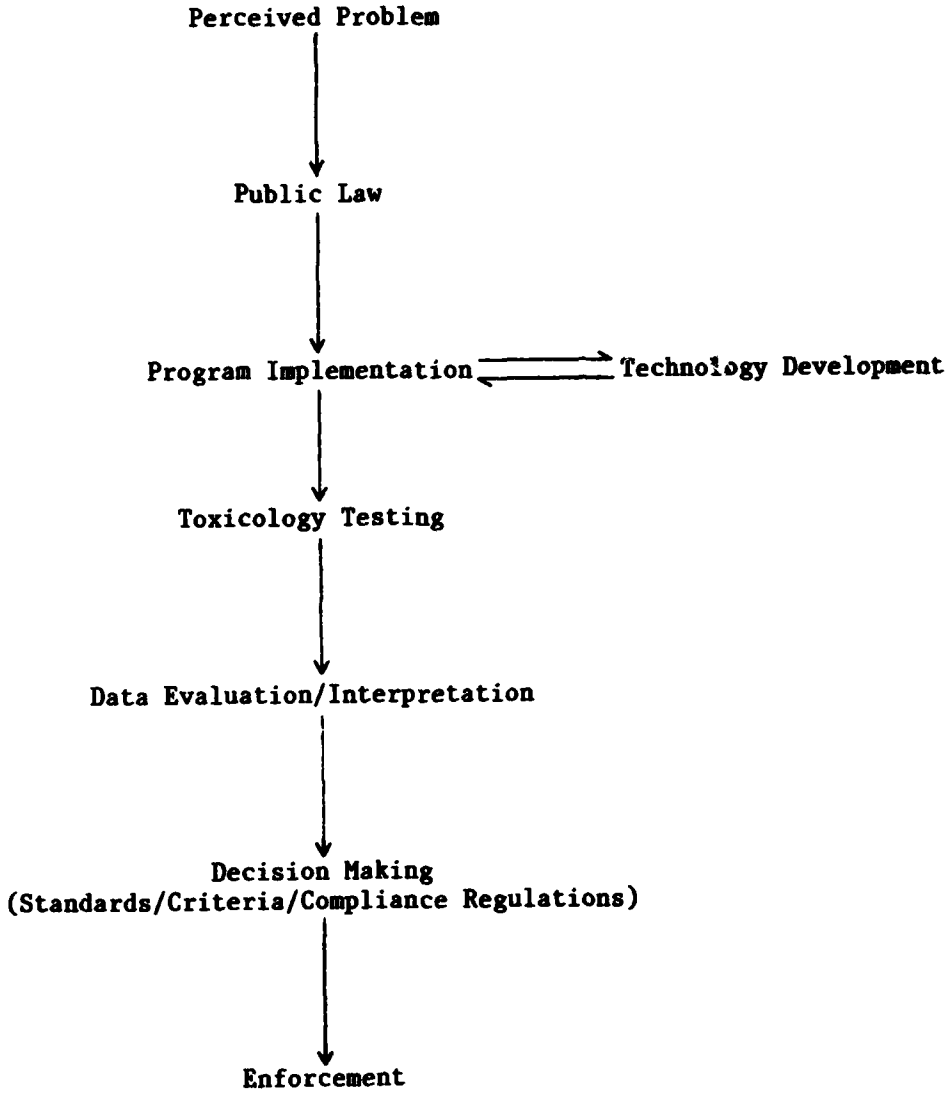

FIGURE 2 GENERALIZED HAZARD ASSESSMENT REGULATORY PROCESS

TABLE 5 INDICATORS OR "FLAGS" OF FEDERAL REGULATORY CHANGES[a]

Indicator or "Flag"	Sources
Executive Branch Policy Change	• Change of Administration • Executive Orders • News Media
Amended Public Law	• Change of Committee Membership • Congressional Committee Agendas and Reports • Congressional Record • News Media
Regulatory Agency Policy Change	• Federal Register • Regulatory Agency Publications/ Reports/Newsletters • Changes in Key Agency Management Positions • Regulatory Agency Reorganization • Court Decisions on Promulgated Regulations that have been Challenged • News Media
Proposed Regulations	• Federal Register • News Media
"Public Comments" on Proposed Regulations	• Professional Societies • Trade/Industry Associations • "Public Interest" Groups • Public Hearings • News Media

(a) Regulatory change is defined as promulgation of the final regulation in the Federal Register. It should not be confused with publication of a proposed regulation which may be significantly modified or never promulgated.

ment level. Some of the major sources of information for each flag are also listed. These represent either direct sources (e.g., Federal Register) where details of the potential change are provided or early warning signals (e.g., Agency reorganization) that indicate an atmosphere for regulatory change may have been created. Similar flags could be identified and monitored at State and local governmental levels if appropriate. In addition, informal coordination within the technical and governmental regulatory communities represents a particularly effective early warning source of pending regulatory changes.

Basis for Forecasting

The basic statutes upon which programs (and agencies) have evolved to implement the desires of Congress represent the foundation for forecasting regulatory changes. A survey of the successes and failures of existing implementation programs and an identification of where and why changes have been made in the past provides direction to where future changes may be anticipated.

It should first be assumed that the basic statutes provide coverage for nearly all significant sources of toxic chemical exposure to humans (foods, drugs, consumer products, workplace, environmental pollutants, etc.). Thus, it is unlikely there will be any major new items of legislation in the foreseeable future that will precipitate new areas of concern (Cywin 1980, 1981). This means that regulatory changes will arise largely from reviews, amendments and refinements of legislation already on the books and "improvements" by the regulatory agency programs responsible for implementing the laws.

One unifying characteristic of the existing legislation and regulations is the common objective of protecting human health. This provides the various regulatory agencies the opportunity for coordination to reduce duplication of effort, and develops uniformity in their use of toxicology technology to support human health hazard decision-making (IRLG, 1979; Anon, 1980d; Gibson, 1980; Laubach, 1980; EPA, 1979a). This commonality of purpose and coordination is not limited to the U.S., in that many other nations are following the U.S. lead by developing human health hazard assessment programs and promulgating regulations dealing with toxic chemicals. Organizations such as the World Health Organization (WHO), United Nations Environmental Programs, the Organization for Economic Cooperation and Development (OECD) and international labor organizations are actively engaged in accumulating data on toxic chemicals and coordinating and promoting human health protection programs on an international basis (OECD, 1979, 1980; Cywin, 1981; Anon, 1979). Thus, there is an atmosphere for changes to unify and expand the use of toxicology technology in the world-wide regulatory arena.

Another unifying characteristic is the overwhelming importance of carcinogenicity in the human hazard assessment decision-making process. No other specific health effect has a stronger impact on the outcome of a compliance regulation than a "positive" finding for carcinogenicity (CEQ, 1975; Doull and Malone, 1980; IRLG, 1979; OSHA, 1980; Peto et al., 1980; U.S. Regulatory Council, 1979). The technology to provide conclusive results here is still in its infancy and relies upon long-term animal studies which are augmented, when possible, by human epidemiological or case history findings. This heavy reliance on long-term animal studies means that toxicology testing is expensive and time consuming. Any regulatory changes that increase testing requirements

must consider the resources (trained professionals, facilities, funding, etc.) required and available. For example, Dr. Richard Hill, Science Advisor to the Assistant Administrator for Toxic Substances, EPA, estimated that there is a world-wide capability to perform only 500 long-term bioassays (for carcinogenicity) per year (Hill, 1981).

It should be noted that there are only six Federal agencies (see Table 6) that have legislative authority and responsibility for establishing human health standards based on chemical toxic effects (Smalley, 1981). Their respective responsibilities to perform or require toxicology testing are quite variable. Some organizations can require the "private" sector to perform toxicology testing. Others must rely on their in-house research programs to provide the data base for standard setting. Still others have no toxicology data development programs and must rely on the work done by others for standard setting. This marks the major distinction between the effects that regulatory changes by each agency will have on the amount and complexity of future toxicology testing.

Each of the major relevant items of legislation is reviewed below to identify the unique aspects associated with the use and need for toxicology data. The discussion under each legislative item includes a summary of the ongoing programs (including research and development) to identify trends that are leading to planned or hoped-for regulatory changes. These discussions are organized under the major headings Environmental Regulations, Occupational Regulations, Food and Drug Regulations and Other Regulations.

Environmental Regulations

There is a large number of legislative mandates covering separate and often overlapping environmental areas of concern with regard to toxic chemical hazards. Table 7 provides a listing and general areas of responsibility of the Legislative Acts that are discussed below. All of these fall under the responsibility of the EPA for implementation.

Reference material for this section was derived primarily from the Public Laws (including their amendments) being discussed. The EPA document, "A Handbook of Key Federal Regulations and Criteria for Multimedia Environmental Control" (EPA, 1979c) provides a convenient summary of these Public Laws. Information on the current EPA administrative, technical and research programs implementing these Laws was derived primarily from the EPA Documents, "Operating Year Guidance for Fiscal Year 1981" (EPA, 1980a) and "Research Outlooks 1980" (EPA, 1980b). Additional sources of information used in this section are specifically cited.

Clean Air Act. The Clean Air Act, as amended in 1977, authorizes a national program of air pollution research, regulation, and enforcement activities. Under the Act, primary responsibility for the prevention and control of air pollution at its source rests with State and local government, with a strong mandate that EPA take action where States do not fulfill their responsibilities. The Federal role is to conduct research and development programs, ensure that adequate standards and regulations are established to meet environmental goals set by the Act, support State and local control activities and ensure that the standards and regulations are effectively enforced.

TABLE 6 FEDERAL AGENCIES RESPONSIBLE FOR TOXIC CHEMICAL EFFECTS STANDARD SETTING[a]

Consumer Product Safety Commission (CPSC)

Environmental Protection Agency (EPA)

Food and Drug Administration (FDA), Dept. of Health and Human Services

Food Science and Quality Service (FSQS), Dept. of Agriculture

Materials Transportation Bureau, Dept. of Transportation

Occupational Safety and Health Administration (OSHA), Dept. of Labor

(a) Source, Ms. Victoria Smalley, U.S. Regulatory Affairs Council

TABLE 7 CATEGORIES OF ENVIRONMENTAL REGULATIONS AND ACTIVITIES LISTED BY LEGISLATIVE ACTS

Legislative Acts Authorizing Environmental Control Activities	Environmental Activities or Categories of Regulations Established
Clean Air Act	National Ambient Air Quality Standards Mobile Source Emission Standards National Emissions Standards for Hazardous Air Pollutants New Stationary Source Performance Standards
Federal Water Pollution Control Act (Clean Water Act)	Quality Criteria for Water National Pollutant Discharge Elimination System EPA Point Source Effluent Standards Toxic Pollutant Effluent Standards Pretreatment Standards Oil and Hazardous Substance Regulations Consent Decree (Settlement Agreement)
Safe Drinking Water Act	National Interim Primary Drinking Water Regulations National Secondary Drinking Water Regulations
Resource Conservation and Recovery Act (Solid Waste Act)	Hazardous Waste Regulations Solid Waste Regulations
Federal Insecticide, Fungicide, and Rodenticide Act (Pesticide Act)	Registration Rules Classification and Use Restrictions Pesticide Tolerance Levels on Agricultural Commodities
Toxic Substances Control Act	Establishment of Interagency Testing Committee Premanufacturing Notification Test Rules Test Standards Regulations on PCBs, Fully Halogenated Chlorofluoroalkanes and Other Chemicals as Appropriate

The environmental goals are generally those prescribed by National Ambient Air Quality Standards (NAAQS). Two types of standards are set: primary standards to protect human health, and secondary standards to protect the public welfare (prevention of damage to property, animals, vegetation, visibility, etc.). The health and other effects are delineated in criteria documents which are the technical basis for developing enforceable standards. NAAQS have been set for total suspended particulates, sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone, hydrocarbons and lead.

In addition to the NAAQS, nationally applicable emissions levels are prescribed for other pollutants deemed especially hazardous and apply to both new and existing pollutant sources. National Emissions Standards for Hazardous Air Pollutants (NESHAPS) have been established for asbestos, beryllium, mercury and vinyl chloride, from a variety of sources. Benzene and radionuclides have also been listed as hazardous pollutants for emissions control.

The EPA's Air Program activities have been primarily directed at the attainment of the primary NAAQS. Although the combined Federal-State-local effort at controlling air pollution has achieved a notable degree of success in improving ambient air quality across the Nation, the standards have not been attained in many areas. The Clean Air Act, as amended in 1977, recognizes this problem and sets forth a comprehensive program for achieving the standards for such areas. The Act now requires that the NAAQS be attained by the end of the calendar year 1982. However, in recognition of the unusual problems some areas will have in attaining the standards for ozone and carbon monoxide, attainment of these standards is to be "as expeditious as possible", but in no case later than 1987. The 1977 Amendments also require New Stationary Source Performance Standards (NSSPS) for all major stationary sources to be set on a specified schedule, more stringent Mobile Source Emission Standards to be set for new motor vehicles and engines and assessments to be carried out related to other standard setting. In addition, a statutory basis is established for Prevention of Significant Deterioration (PSD) which is, in effect, a mechanism for managing the air quality impacts associated with economic development.

In 1981 considerable effort is being devoted to developing the data base required for the State Implementation Plans (SIP). A review of all NAAQS required by the Clean Air Act was ongoing in 1980 and may result in new or altered standards being proposed in 1981 for oxides of nitrogen, carbon monoxide, sulfur dioxide and suspended particulates. During 1981, it is also planned to increase the promulgation of NSSPS consistent with the Clean Air Act requirements. These new emission limits, in addition to limiting emission from new sources to levels achieved by "best available adequately demonstrated technology," will also provide a basis for determining required case-by-case levels of control for sources subject to PSD.

With specific regard to toxicology testing requirements, the EPA is in the process of adopting an Air Carcinogen Policy. Health assessments will be made of additional air pollutants and appropriate regulatory actions (formulation of new or revised standards) taken under the guidance of this policy. Thus, additional NESHAPS are also to be promulgated in 1981. As the requirement for identifying additional hazardous air pollutants is expanded, some additional toxicology needs will be levied on the existing resources. The rate of progress

for this, however, remains rather static for the next few years due to budgetary restrictions. This is because EPA has no authority under the Clean Air Act, to require the "private" sector to perform toxicology studies in support of developing air pollutant standards.

Under their in-house research and development (R&D) programs EPA will continue to define the adverse health and environmental effects of airborne pollutants, describe the ways in which these pollutants are transported and transformed in the atmosphere, and develop and evaluate pollution control technologies. Field studies in urban areas, to identify hazardous pollutants present, are being initiated. This information will be used to help develop hazardous pollutant regulatory strategies under Section 112 of the Clean Air Act and to determine compounds to be screened for carcinogenicity and other toxic effects. Therefore, the health effects research program will continue to focus on methods to more accurately determine actual human exposure to air pollutants and to better define the toxic effects of these pollutants to real world population.

In the mobile source area, evaluations of health effects from diesel engine emissions will continue. In the stationary source area, the subject of acid rain and its ecological and human health effects will be expanded. The health effects research program is and should be expected to concentrate on air pollutants that are common to many industrial and domestic activities. Health hazard research on specific air pollutants from limited numbers of sources (for NESHAPS) will be limited and on a case-by-case basis.

Clean Water Act. In 1948, the Federal Water Pollution Control Act (FWPCA) was passed. It provided limited Federal authority while primary control and enforcement authority remained with the States. It did not address the toxicity of chemicals as a specific data requirement in establishing water quality limits. It was not until 1965 and 1966 that significant amendments to the Act were made which provided for national water quality standards, with enforcement responsibility thus shifting from the States to the Federal government. The water standards, again, were not oriented toward the toxic effects of specific pollutants. Rather, the amended Act required control of generic pollutant categories to reduce general environmental degradation and to improve the aesthetic properties of the Nation's waters.

In 1972, major national goals were created, by a further amendment for "the restoration and maintenance of the chemical, physical and biological integrity of the Waters of the Nation." The EPA was given the responsibility to make the waterways of the U.S. "fishable and swimmable" by July 1, 1983. This was to be achieved by controlling all point sources of pollution through national permits based upon national industrial effluent limits and secondary treatment (for Publicly Owned Treatment Works (POTW's)) or upon water quality standards -- whichever are the more stringent. The national industrial effluent limits are to be based upon achievable technology, not toxic effects.

The first specific requirement to address toxic effects and, therefore, develop toxicology data was provided by a separate section of the 1972 Amendments to this Act which required national limits on "toxic" pollutants. The EPA was not able to implement that section of the Act due to a lack of technical (toxicology) data to cover the multiplicity of pollutant and human exposure

situations. Mr. Allen Cywin, retired Senior Science Advisor, Office of Water and Waste Management, and Director of the EPA Effluent Guidelines Division during this time period, instead proposed that the Effluent Guidelines Program be expanded to include toxic limits based upon achievable technology (Cywin, 1981). This idea became the subject of a court-ordered consent decree, covering 21 industries and 65 families of toxic pollutants, which was later embodied into the Law in 1978 (when the Act was again amended and retitled "The Clean Water Act"). Thus, through litigation the EPA was required to make use of an acknowledged limited toxicology data base to promulgate Ambient Water Quality Criteria. The fact that these criteria are promulgated to serve as the technical basis for enforceable standards and regulations indicates a trend to develop regulations that are subject to significant modification as more complete toxicology data become available.

As a result of these events, the emphasis on controlling toxic pollutants will encompass nearly every aspect of the EPA water program in the future. Specific programs and/or activities which support this trend are as follows:

1. During 1981 and beyond, the EPA will largely accomplish the task of standard setting for the 65 toxic pollutants. The promulgation of Best Available Technology (BAT) regulations required by the "Court Agreement" should be completed for discharge permits written during the 1984-1987 time frame. Increased attention will also be given to determine whether there are additional toxic pollutants which should be addressed in effluent guidelines, and special "hot spot" studies will determine whether controls in addition to BAT are necessary.

2. Completion of the BAT regulations will allow a shift in emphasis to investigation of "innovative" technologies to minimize the overall discharge of toxic chemicals into the environment. Pretreatment of toxic compounds by indirect discharges to POTW's will receive increased emphasis in the 1980's. The water quality monitoring programs will provide pollutant-by-pollutant control strategies based on assessments of environmental distribution/fate and exposure/risk analyses for the 65 toxic pollutants, as well as developing area-by-area regulatory strategies as guidance to the States where BAT may not be adequate.

3. Control of toxic pollutants under the Clean Water Act will also address discharges into surface waters caused by spills, leaks and similar non-routine occurrences. The promulgation, in late 1979, of revised regulations designating hazardous substance and reportable quantities under Section 311 of the Act allows EPA to continue to expand its spill prevention and emergency response program. These latter activities are being folded into the "Superfund" Act which was enacted in December, 1980, and which provides funds for emergency clean-up of abandoned hazardous waste sites.

Under the Clean Water Act, the EPA has no authority to require the "private" sector to perform toxicology testing on water pollutants. Such data must be developed under the EPA's R&D programs or through cooperative agreements with other programs having similar data base needs. Under the EPA's R&D program, increasing emphasis will be placed on the behavior (fate) of toxic pollutants

and their effects on human health and the environment. These activities are categorized as: health effects research, environmental processes and effects, measurement and monitoring, and industrial and municipal research. Health effects research will address the health implications of existing and new technology for the treatment, disposal and reuse of wastewater and sludge. It will also continue to expand the toxicology data base for the 65 priority toxic pollutants in complex effluents. Finally, the program will develop recreational freshwater quality criteria for potable, industrial and aquacultural purposes. Although present planning for adding additional toxic water pollutants to the list of 65 is advanced, budget restrictions during the next few years will severely limit new initiatives.

Safe Drinking Water Act. Assuring the safety of drinking water is primarily the responsibility of the State and local governments. However, Congress provided that the Federal Government share in this responsibility through national standard setting and providing assistance and reinforcement for State and local efforts to protect the integrity of public water supplies. Prior to the passage of the Safe Drinking Water Act (SDWA) in 1974, the Public Health Service Act and the Interstate Quarantine Regulations provided the only statutory authority for the Federal drinking water program. With the enactment of the SDWA, the EPA's authorities and responsibilities were significantly increased. The Act, as presently amended, required the EPA to develop and promulgate national drinking water standards. It also established two major programs. The Public Water System Supervision Programs (PWS), which is designed to ensure the safety of drinking water provided by public water systems, and the Underground Injection Control Program (UIC), which is designed to protect present and future underground sources of drinking water from contamination through injection wells.

There are primary drinking water regulations which specify Maximum Contaminant Levels (MCL's) to protect the public health, and secondary drinking water regulations which deal with aesthetic quality. Interim primary drinking water regulations, which cover bacteria, turbidity, and certain inorganic chemicals, pesticides and radionuclides, have been in effect since June 1977. These standards were revised in 1979 to regulate chloroform and other trihalomethanes (EPA, 1979b).

The EPA Drinking Water Program will develop additional MCL's for specific drinking water contaminants, revise existing standards to incorporate new data, and develop a regulatory approach to control contaminants which may increase the incidence of cardiovascular diseases. In addition, UIC regulations are currently being promulgated and a ground water protection strategy is well along in its development.

In 1981 the Drinking Water Program will focus on the establishment of Revised National Primary Drinking Water Regulations which are to include MCL's for 10 additional organic chemicals and MCL's or treatment requirements for 10 additional inorganic chemicals, virus and protozoa. The longer-range goal and overall concept of the R&D program is the provision of a scientific basis for assuring safe supplies of drinking water for the people of the U.S.

The program is composed of three main disciplinary types of research: health effects, control technology (including ground water) and quality assurance.

In the health effects area, the research will emphasize the potential carcinogenic properties of organic contaminants, especially chlorinated hydrocarbons associated with disinfection practices. This part of the program supports chronic toxicology and epidemiology studies, as well as shorter-term toxicology studies for priority organic compounds, where comprehensive data is needed for setting MCL's. The health effects program also emphasizes cardiovascular effects from inorganic contaminants and gastrointestinal illnesses related to microbial contaminants. All health effects research here is supported by EPA funding because the drinking water program has no authority to require testing by the "private" sector.

Solid Waste Act (Resource Conservation and Recovery Act). The extent and severity of hazardous waste management problems have focused the attention of Congress and the public on the needs for nationwide regulations. EPA statistics indicate the annual generation of municipal and industrial wastes totals almost 500 million metric tons. This includes 54 million metric tons of hazardous wastes such as toxic chemicals, pesticides, acids, caustics, flammables and explosives. Only 10% of these are currently disposed of safely. With the curtailment of emissions to air and water due to other environmental laws, the EPA estimates the amount of hazardous waste will grow by 30% in this decade.

The Resource Conservation and Recovery Act (RCRA), now known as the Solid Waste Act, established the first national program to protect human health and the environment from the damages caused by improper waste management practices. The EPA has now promulgated a list of hazardous waste materials, criteria for defining wastes as hazardous, standards for generators and transporters, standards for hazardous waste treatment storage and disposal facilties, regulations for facilities permits, and regulations for the development of State hazardous waste programs. The "cradle-to-grave" manifest system for tracking hazardous wastes went into effect on November 19, 1980.

In the near future the EPA will move into the implementation phase of the hazardous waste program. Two phases of interim authorization for State hazardous waste programs will begin, the first phase introduced by interim status standards (for permitting sanitary landfill sites), and the second phase keyed to the effective date of the technical standards for hazardous waste facilities. Each phase will allow States two years to upgrade their hazardous waste programs to meet the authorization requirements. While RCRA provided for and encourages authorization of States to operate the hazardous waste regulatory programs, it also requires the EPA to operate the programs for those States that do not seek or are unable to obtain authorization.

EPA R&D activities in support of RCRA will assume a new double focus in order to: (1) provide a firm scientific basis for the RCRA regulations and the permit guidelines; and (2) accelerate development of techniques for investigation, remedial treatment, and containment to support the uncontrolled hazardous waste site programs. This research program will include some limited toxicology testing to support the listing and de-listing of hazardous wastes and to provide specific health effects data for priority chemicals from "hot spot" hazardous waste sites. This effort will require coordination with toxicology work done by other EPA programs and other Federal Agencies. This is because there is little funding recognized under RCRA to support toxicology testing and because the EPA does not have the authority to require "private" sector testing under the Act.

Pesticide Act. The Federal Pesticide Act of 1978, formerly known as the Federal Insectide, Fungicide and Rodenticide Act (FIFRA), provides authority to establish regulations to protect human health and the environment from the use of pesticides. The objective of the EPA's pesticide program is to protect the public health and the environment from unreasonable risks while permitting the use of necessary pest control technologies. This objective is pursued through four principal means: (1) review of existing and new pesticide products, (2) use management, (3) enforcement and (4) research and development.

New pesticide products are reviewed and registered upon a finding that the product will not pose unreasonable risks to humans or the environment, taking into account the potential benefits. Risk is often quantified in terms of the numbers of, or probability of, certain health effects occurring in a given population. Benefits are most often stated in dollar valuations of such factors as increased crop yields, lower food costs, reduced chances of diseases or the cost savings with respect to the use of alternative pest control measures. Prior to registration, the benefits of a particular pesticide must be demonstrated to exceed the risk.

Most existing pesticide products were registered before the impact of chronic effects (e.g. cancer, birth defects, gene mutations, etc.) of exposure to toxic chemicals were well understood and before long-term toxicology testing was routinely required. Their reregistration will thus require more thorough and consequently more resource intensive reviews of all test data for both acute and chronic effects. Under FIFRA, the EPA can request industry to supply this information for old products. However, because of economic and political considerations, this authority has been used very sparingly in the past and that mode is predicted to continue (Cywin, 1981). Thus, there will be only a slight increase in the demand on "private" sector toxicology testing resources in the years ahead to review these existing pesticide products.

In the past, registration entailed an examination of risk for each product, i.e., each specific formulation. The EPA is now developing a generic pesticide registration program. Generic registration entails a single, comprehensive evaluation of the risks and benefits of the active chemicals that are common to numerous products. For every pesticide and its formulations, performance standards and safety criteria will be set, to which registrants must adhere in order to register and reregister products. In addition, standards for registration will state tolerable levels of exposure for foods, consumers, field workers, applicators, and other persons and organisms unintentionally exposed to the pesticides. In order to develop these tolerable levels a significant amount of toxicology testing will be required. These toxicology testing requirements will be largely satisfied by EPA-funded testing.

This program will most directly impact the public health and the quality of the environment through the imposition of a variety of pesticide use restrictions. The EPA's regulatory options under FIFRA range from cancelling specific uses to unconditional registration. Where unreasonable adverse effects are identified, the Agency may initiate Rebuttable Presumption Against Registration (RPAR) proceedings, in which suspect chemicals are subjected to a focused risk/benefit assessment and alternative chemicals are considered. In cases where a lesser degree of hazards may exist, the EPA may consider such risk reducing measures as: precautionary labeling, childproof packaging, restrictions to use by certified applicators, and mandated use of protective clothing.

The R&D program supporting the EPA's pesticide regulatory activities includes the development of data required to support administrative reviews and litigation. Such data are required on the major classes of pesticides now registered and in common use, as well as chemicals considered as possible substitutes for cancelled pesticides. The program places emphasis on three basic elements necessary to evaluate overall human health and environmental hazards from pesticides: (1) identification of populations at risk, (2) assessment of individual exposure and (3) determination of adverse effects.

Exposure assessment research will improve and develop protocols to determine occupational exposure to pesticides through their use, determine potential exposure of the general population to pesticides in air, freshwater, coastal waters, soil, sediment, plants, and fish and animals. As increased amounts of exposure assessment data become available, it will be possible to make more accurate and meaningful identification of overall populations at risk. Registrants (industry) have provided much toxicology data on the adverse effects of pesticides. Although there is a continuing need for such data, particularly for new compounds, the highest research priority is being placed on gaining improved exposure assessment data. This is an area where EPA R&D efforts are likely to stimulate technology changes during the next decade.

Toxic Substances Control Act. The Toxic Substances Control Act (TSCA), enacted in 1976, establishes a program to identify the effects of chemical substances and mixtures on human health and the environment. It further provides for regulations to reduce risks for those chemicals which present an "unreasonable risk" of injury to human health or the environment. The Act's coverage is broad, encompassing nearly 47,000 chemicals currently in commerce and the several hundred new chemicals introduced each year. About 115,000 manufacturers and processors of chemicals are subject to the Act.

The major programs the EPA is developing to implement the Act are those to: (1) require toxicology testing of chemicals and submission by industry of reports containing existing information for chemicals currently in use, (2) review data and act on new chemicals and significant new use notifications submitted by industry, (3) develop and enforce statutory and regulatory programs for existing and new chemicals that pose "unreasonable risks" to human health and the environment and (4) conduct research to support implementation of the Law.

Major implementation programs (currently under development) will include a hierarchical scheme of toxicology Test Standards to provide uniform procedures for the generation of health and environmental effects data. Additional programs are being developed to define the use of toxicology data in regulations. This involves a multi-stage assessment process for reviewing suspect chemicals to determine potential risks; control regulations on chemicals posing unreasonable risks; premanufacture review for new chemicals; approaches for using reporting requirements for information gathering; and mechanisms for setting priorities for action, enforcement policies and procedures for inspections, hearings, penalties, emergency actions and imports.

Proposed Test Standards which have been issued (to be finalized during 1981) include standardized requirements for Good Laboratory Practices (GLP) during health effects testing, chronic toxicity (carcinogenicity), acute and subchronic

toxicity, mutagenicity, teratogenicity, reproduction effects and metabolism studies (EPA, 1979a). Additional Test Standards, to include neurotoxicity and behavioral effects, are currently under development.

The EPA's research programs in support of TSCA will focus on developing improved rapid, reliable, and cost-effective techniques to be used for predicting the transport, exposure and adverse effects on human health and the environment for toxic substances. Under this program the EPA plans to accelerate the development and validation of new and promising technology for screening toxic substances. Thus, the principal objectives of EPA-supported toxicology research is to (1) provide screening data for developing priorities of which chemicals should receive emphasis under TSCA and (2) provide standardized procedures for use by industry when performing toxicity studies under a Test Rule.

It must be emphasized that the statutory provisions of TSCA have the greatest potential for increasing the toxicology testing workload in the "private" sector. This potential workload has not been fully realized because the TSCA implementation programs are still being developed. During the next three to five years a large number of Test Rules will be issued by the EPA to require toxicology testing by industry. It was expressed by Dr. Herbert Blumenthal, Director, Division of Toxicology, FDA, that in anticipation of this increased workload many industries are rapidly developing/expanding their in-house toxicology capabilities (Blumenthal, 1981). Dr. Blumenthal felt that, if implemented to the letter of the law, TSCA alone could require dedication of all existing toxicology laboratory facilities for the next 25 years.

Occupational Regulations

Control of human health hazards in the workplace is the responsibility of the OSHA, under the DOL. That organization represents the regulatory arm for establishing and enforcing regulations dealing with worker safety from all hazards (i.e., fire, accidents, hearing and eye hazards, etc.) not just the effects following exposure to toxic chemicals. The National Institute for Occupational Safety and Health (NIOSH) provides technical support to OSHA to implement its responsibilities under the Occupational Safety and Health Act of 1970.

The Act authorizes the development and enforcement of standards for safe and healthful work conditions and for protection against workplace toxic substances. OSHA provides assistance to the States to develop workplace safety and health programs and provides funding for research and education in the field of occupational safety and health.

On January 22, 1980, OSHA promulgated its final rulemaking on "Identification, Classification and Regulation of Potential Occupational Carcinogens" (OSHA, 1980). Anticipating a legal court challenge, the rulemaking document reads more like a legal brief than a scientific document. It provides the reader with an insight into the growing difficulties facing the regulatory agencies when dealing with toxic substances.

The rulemaking document comments that OSHA is in a "regulatory dilemma". Any decision as to how to regulate carcinogens is obviously complex. "Despite some advances in our understanding of cancer, the fundamental causes and

mechanisms elude us. Chemical or physical agents known or suspected to pose a risk of producing cancer in humans present certain problems unique to the regulation of toxic materials in the workplace. And with the increasing number of environmental chemicals, the number of carcinogens is also likely to increase, together with the size and complexity of OSHA's rulemaking and the concomitant records and related issues consistently raised in various federal Courts of Appeals."

Further on, the OSHA regulation notes, "Occupational carcinogenesis is the result of failure to detect carcinogens in the laboratory before there is exposure of human populations, and in some cases failure to take adequate protective measures even after a carcinogenic risk has been identified". This, of course, will only lead to the need for more and better toxicology to support standards for carcinogens (and other toxic chemicals) in the workplace.

According to Dr. Ken Chu, Special Assistant to the Director of the Health Effects Division, OSHA, the Agency does not have the financial resources to meet its needs for toxicological testing (Chu, 1981). They sponsor testing at NIOSH for 5-6 individual chemical standards per year. Therefore, their regulations are primarily based upon identification and documentation of work done by others and by the National Toxicology Program (NTP) of U.S. Department of Health and Human Services (formerly DHEW).

Food and Drug Regulations

Food and Drug Administration. Under the Federal Food, Drug and Cosmetic Act (FFDCA) the Food and Drug Administration (FDA), U.S. Department of Health and Human Services has pre-clearance responsibility for releasing drugs, veterinary medicines and food additives to the marketplace. Their laboratories develop methods, certify other laboratories and check on the data supplied by industrial sources. For example, the FDA establishes tolerance levels and exemptions from the requirement of a tolerance for pesticide residues in or on raw agricultural commodities and processed foods. These tolerance levels protect the public health while giving appropriate consideration to food production. Determination of tolerance involves careful review and evaluation of residue chemistry and toxicology data to ensure that the maximum residue levels likely to be found in foods are safe for human consumption. Included in this consideration are the cumulative effects of substances having similar pharmacological properties.

The FDA provides most of the funding support for the NTP at the National Center for Toxicological Research in Arkansas. Their efforts there are primarily directed toward developing better toxicology data for drugs and food additives that were previously cleared, but now are suspected to possess serious toxic properties. The FDA feels that this review program will be very slow due to resource restrictions (Blumenthal, 1981). The FDA continues to require industry to perform testing and submit data for new compounds. Dr. Herbert Blumenthal, Director, Division of Toxicology, FDA, notes that the FDA's program "is small potatoes" compared to TSCA. Thus, the demand for toxicology testing resources is unlikely to be altered significantly to meet future changes in FDA regulations (Blumenthal, 1981).

Food Safety and Quality Services Administration. The Food Safety and Quality Services Administration (FSQS), under the USDA, is responsible for meat, poultry and fish inspection services to assure that these foods are safe, wholesome, nutritious and of good quality. According to Dr. John Spaulding (Director of Research, Evaluation and Inspection under the Deputy Administrator for Science, FSQS) the FSQS inspects food for signs of carcinogenic agents among other toxic chemicals (Spaulding, 1981). Dr. Spaulding indicated that they rely on FDA and EPA tolerance levels for their standards. Thus, the FSQS supports no toxicology testing.

Other Regulations

This section provides a brief summary of the relevant regulatory activities associated with the CPSC and the Materials Transportation Bureau (MTB) of the DOT.

Consumer Products Safety Commission. Under the Consumer Products Safety Act, the CPSC has some authority for the protection of humans from carcinogens and other toxic compounds. According to Dr. Richard Hill, Science Advisor to the Assistant Administrator for Toxic Substances, EPA, it has never utilized that section of the Act that can require "private" sector toxicology testing (Hill, 1981). It is not predicted that CPSC will exercise this authority under the new Administration because of the anti-regulatory mood. Therefore, the CPSC represents a user of toxicology data but not a major generator of testing requirements.

Materials Transportation Bureau. Under the Hazardous Material Transportation Act, the MTB utilizes available toxicology data to formulate and coordinate regulations dealing with the transport of toxic and hazardous chemicals. According to Victoria Smalley, U.S. Regulatory Council, the MTB does not conduct or require toxicology testing (Smalley, 1981). As with the FSQS, the MTB depends upon the work performed by others to provide the technical basis for its regulations. As this activity is concerned primarily with the safe transport of relatively large quantities of toxic chemicals, their toxicology data needs are for the acute effects and long-term effects (carcinogenicity) resulting from relatively short-term exposures.

Factors Influencing Regulatory Changes

The following provides an analysis of the major factors that are anticipated to influence toxicology testing regulations (primarily at the Federal level) during the next decade.

Political Aspects

Although political influences should reflect the consensus opinion of the entire population, this analysis will be restricted to political influences from the Executive Branch (e.g., the new Reagan Administration) and from Congress. The following is a listing of forecasting statements and brief discussions of political factors that are likely to impact toxicology-related regulations:

1. The new Administration will attempt to slow down and possibly rollback a number of "end-point" compliance regulations. There are several factors that support this forecast. Probably the most important is the fact that President Reagan's campaign was strongly based on reducing the regulatory power of the Federal Government and returning much of this responsibility to the States. In this regard, President Reagan will attempt to represent the over-regulation backlash that has developed over recent years.

2. President Reagan's regulatory focus will be primarily toward the "end-point" compliance regulations mandated by Congress and not toward regulations that will necessarily decrease toxicology testing. Mr. Livermore, who headed up the transition team for the EPA, was reported to have noted to then President-Elect Reagan that the EPA's rate of progress was dictated by legislative mandates and court orders related thereto, and not by over zealousness (by the EPA's staff) as some critics have charged (Cywin, 1981).

3. The Reagan Administration will, through the appointment of administrators, influence regulatory decision-making in many areas. Mr. Steven Jellinek, the EPA's outgoing Assistant Administrator for Toxic Substances, was quoted as saying that "the close decisions will be made on the basis of economics and not risk aversion" (Greve, 1981). This again points to President Reagan's focus on "end-point" compliance regulations. These "end-point" regulations tend to create the greatest amount of reporting requirements for industry and have the greatest economic impact on those affected. Influences that change the ultimate outcome of decision-making during the regulatory process (Figure 2) do not necessarily diminish, and may increase, the demand for data (toxicology, economic, etc.) to support the decision-making processes.

4. Congress will moderate legislative compliance deadlines in light of prevailing energy, economic and political factors. The first law up for review by Congress is the Clean Air Act. Some deadlines may be stretched out and some of the "command control" requirements may be replaced by performance standards. The report of the National Commission on Air Quality, due at the end of March, 1981, may provide more specific details of likely changes to that Act.

   Regardless, Senator Stafford (R-VT) is the new Environmental Committee chairman. He is a moderate and worked well in the past for environmental legislation including the present Act. It is expected he will not approve any major butchering of the Clean Air Act. Also, there should be little or no effect on the Act's present requirements for toxicology testing, whether or not its provisions (for compliance) are moderated. It is also believed that the Senate Committee will have its hands full with the Clean Air Act for this next session of Congress (Cywin, 1981). Thus, it is not expected to tackle major changes in other environmental programs during that period. The second Act likely for Congressional review is the Clean Water Act. Assuming this review will take an additional two years (total of four), it is unlikely that the TSCA (the one responsible for the

greatest amount of "public" sector toxicology testing) will receive any significant attention by Congress until the middle of this decade.

5. Neither the Administration or Congress is likely to cause significant changes in the occupational health legislation. Although OSHA has been very unpopular in industry, its provisions are heavily supported by organized labor. In fact, a recent Washington Post article reported on a meeting between key organized labor officers and Senator Orin Hatch (R-UT) (Cywin, 1981). It was reported that the labor officers were successful in getting Sen. Hatch to moderate his prior open hostility to the Act by promising to press for strict regulations only on major health effects problems, rather than the perceived "nitpicking" of past years.

6. To control Government spending, the Reagan Administration will try to limit in-house R&D budgets, including those for health effects research. This will be a continuation of the budget cutting that took place in the Fiscal Year (FY) 81 budget by the Carter Administration. For example, within the EPA's Office of Research and Development, FY 81 budget cuts will require a nearly 1/3 reduction in staff (at the headquarters level) and the deletion of several health effects research programs (Ulvedahl, 1981). This may cause a regulatory decision-making dilemma, in that the R&D programs may be unable to generate data at the pace desired by the Administration to support improved risk/benefit analyses needed to justify rollbacks or moderation of regulatory compliance deadlines for specific health standards.

Public Involvement

The major public pressure factors likely to influence toxicology-related regulations follow:

1. The amount of public interest and support for health related standards will remain high. By regulatory agency design, public comment periods are built into nearly all rule-making processes. Recent examples of such public participation were the large amount of public comments that were received by the EPA during the development of Ambient Water Quality Criteria for the 65 priority pollutants, the proposed Test Standards under TSCA and the Interagency Regulatory Agency guidelines for toxicity testing (CMA, 1979, 1980a, b, c; Conservation Foundation, 1978). It should be noted, however, that many of these "public" comments often represent comments from industry, trade organizations or scientists employed by those organizations. Thus, public comments during the regulatory process may often represent the opposing pressures from public and industrial groups.

2. In general, continued public support for health effects regulations will help diminish major rollbacks of the relevant regulations. Types of public involvement included here are: pressures from organized labor unions, consumer groups and special interest groups such as the Sierra Club, the National Resources Defense Council, and the

Environmental Defense Fund. An example of the influence such groups have was the court order that forced the EPA to establish Ambient Water Quality Criteria for 65 classes of toxic water pollutants in accordance with the deadline mandated in the 1972 amendments to the FWPCA. Continued use of these legal mechanisms is likely to require regulatory agencies to meet the compliance schedules established by Congress. The key point here is that the compliance dates must be first altered by Congress before this form of public pressure (as assisted by the courts) can be alleviated.

Industry Pressures

The major factors associated with industry pressures are:

1. Industry will exert increased influence on regulatory changes in the next decade. In the recent past, industry influence has not been sufficient to forestall enactment of the major items of legislation that they opposed. Two major recent examples of industry's increasing strength, however, are quite evident. First, the Reagan Administration openly reflects a more favorable attitude towards the economic problems and "over-regulated" concerns of industry (e.g., the January 28, 1981 deregulation of oil prices). Therefore, the Executive Branch represents a more powerful advocate for industry than in the past. Secondly, industry did significantly influence a "watering down" of the Superfund Act to provide funds for the cleanup of abandoned hazardous waste sites.

2. Commercial interests will continue to make heavy use of litigation proceedings to delay regulatory compliance deadlines. As discussed earlier, the cost of ultimate compliance (pollution control, waste treatment/disposal, etc.) is the key issue with most industries. One of the major arguments by industry to have a regulation set aside or delayed is based upon inadequate health effects findings. Where industry prevails in these litigation issues, a requirement for more data (more toxicology testing) will be generated. Mr. Allen Cywin, while with the EPA, found that industry would often volunteer to initiate or continue toxicology and related health effects research in order to postpone compliance with a regulation that was believed to be scientifically unjustified or had major economic consequences (Cywin, 1981).

International Aspects

The major international factors having a potential impact on toxicology testing are:

1. Many foreign countries have enacted health and environmental laws similar to those in the United States. This has caused increased competition for world-wide toxicology testing resources. The OECD has an ongoing program to "harmonize" test protocols among its members. The members of OECD include: the United States, Western Europe, Canada and Japan. The coordinated protocols developed are

not binding on the sovereign governments but are believed to be generally followed (Cywin, 1981; OECD 1979, 1980). The European Economic Community has a similar coordination program. These international programs will have two significant impacts on toxicology testing:

a. There will be additional short-term competition for scarce toxicology resources, including trained professionals and facilities. This trend will be increased because the testing requirements of TSCA will apply to foreign manufacturers who wish to export chemicals to the United States.

b. There will be a long-term reduction in the amount of U.S. supported toxicology testing required to meet U.S. regulatory agency requirements. Through this international coordination, toxicology data generated in foreign countries will increasingly meet the U.S. technical and quality assurance requirements, thus becoming more acceptable for use in U.S. regulatory decision-making.

2. Compliance regulations formulated by other nations should not have a major influence on U.S. regulatory decisions. One reason for this is because most foreign nations have modeled their programs after their U.S. counterparts. Therefore, their organization and approach to human health hazard assessments is lagging behind those established in the U.S. Secondly, the social, economic, and political factors influencing decision-making in foreign nations are different from those in the U.S. For example, many developing countries have a greater demand for food than for protection of the population from a carcinogenic pesticide. The average lifetime in many countries is too short to place a high priority on long-term chronic disease problems.

Technology Changes

Technology changes are discussed here because of their potential for causing regulatory changes and influencing the pace of such changes. (See the section entitled "Impact of Technology Changes" on p. 61) for a more thorough discussion of changes anticipated in toxicology testing technology over the next decade.)

1. Although the EPA and other organizations are developing alternative, less expensive testing methods, health effects standard setting will continue to be based on animal testing for the next decade. Use of screening toxicity tests and possibly, biochemical structure-activity relationships to predict human health hazards, will require years of additional testing and validation to provide the same type of acceptable predictability for regulatory purposes provided by current animal testing methods. As indicated by Dr. Hugh McKinnon of the EPA's Office of Research and Development, toxicology testing will require increased development of testing procedures for long-term animal studies so that better threshold data can be obtained (McKinnon, 1981).

2. Advancements in testing technology are likely to stimulate new regulations for more specific types of toxicology testing. More specific testing generally means additional testing has to be done to supplement those types of tests that are currently part of the state-of-the-art. The acceptance of technology advances (screening tests, structure-activity relationships, etc) to actually reduce the amount of toxicology testing per compound is many years away.

3. An important technology issue is the impact that current and anticipated regulations have on technology developments. Regulations governing toxicology testing tend to reduce the amount and rate of new technology developments. As expressed by Mr. Gerald Laubach, President of Pfizer, through "excessive formalization and standardization" of the research required for marketing a new drug "the Food and Drug Administration regulates the process of innovation per se." He feels that this "state-mandated scientific orthodoxy" has become a critical factor in "the interpretation of long-term animal toxicology experiments, the design of clinical studies and the evaluation of the results from them." Further, Mr. Laubach argued "that the chemical industry (subject to TSCA regulations) hasn't begun to feel the effects of a mature and fully functional regulatory system." This final statement is specifically relevant to the Test Standards (standardized testing procedures/protocols) and the Test Rules (regulations requiring industry to perform toxicology testing) that will be forthcoming from the EPA under TSCA.

Economics

Economics has been a supporting and often controlling consideration in nearly every prior discussion. With the present overwhelming influence of economics on our society, this factor will have a major influence on future toxicology testing regulations as well as the resources needed to meet the regulatory requirements.

1. Greater weight will be given to economic factors during decision-making leading to compliance regulations. This will include the actual costs for compliance (costs for pollution control, costs for developing replacement chemicals in commerce, etc.) as well as the loss of benefits the chemical would provide to society (increased food production (in the case of pesticides), energy saving insulation (e.g., asbestos), or light weight construction materials (such as PVC, etc.)) Mr. Steve Jellinek, outgoing EPA Assistant Administrator for Toxic Substances, predicted "the close calls will be decided in favor of economics instead of risk-aversion" (Greve, 1981).

2. Human health and "quality of life" risks and benefits will have to be expressed in economic terms to permit economically sensitive risk-benefit analyses. New techniques in performing risk-benefit analyses will need to be developed and will lead to further slow-downs and confusion in promulgating new regulations. Techniques are not available to quantify many risk-benefit analysis inputs in strict economic terms. Health care costs (due to exposures to toxic

chemicals) and food costs (due to restrictions on the use of pesticides) are examples of factors that can be estimated now. Factors, such as the cost of a human life, will require subjective estimations of dollar values and will initiate controversy and confusion. The costs and time for development of this "new economics" for risk-benefit analyses and the data gathering to support decision-making will lead to further delays in new regulation decision-making.

3. The "new economics" based risk-benefit analysis techniques will require more definitive toxicology testing in order to define threshold levels for toxic effects. This is already the case for carcinogenicity where a qualitative "yes" or "no" result is no longer satisfactory. Rather, a quantitative probability estimate of the human cancer incidence due to exposure to the chemical is now required for regulatory decision-making. It should follow that similar requirements will be established for other types of toxic effects. With decisions being made in favor of economics rather than risk aversion, it will be necessary to quantify the amount of residual risk. Therefore, the "end-point" regulation (specific health standards or criteria) may no longer be based on the "no-effect" level.

4. Limitations in overall Government spending will force the regulatory agencies to focus on only the highest priority human health hazards. A trend away from the across-the-board comprehensive hazard assessments is already evident. OSHA will concentrate on only 5-6 priority workplace contaminants per year (Chu, 1981). The FDA's review of previously registered food additives and drugs will be "slow due to resource restrictions" (Blumenthal, 1981). The EPA's health effects research budget was cut in FY 81 in spite of the growing needs in this area (McKinnon, 1981).

5. General restrictions in Government spending will force greater coordination and collaboration between Government agencies and the "private" sector to satisfy toxicology testing requirements. Increased reliance on the NTP under the Department of Health and Human Services (HHS), to meet the toxicology requirements of the OSHA, the FDA, the CPSC and, to a somewhat lesser extent, the EPA should be anticipated for toxic compounds of common concern (Hill, 1981). A reduction in the adversary relationship between the regulatory agencies and industry should result from the reduced Government funding for generation of scientifically defendable data needed to back up regulatory goals and objectives.

6. A greater number of highly qualified health professionals will leave Federal service for higher paying jobs in the "private" sector. As industry rushes to establish toxicology testing capabilities to meet TSCA requirements there will be a selective demand for the best talent available (Blumenthal, 1981). Dr. C. C. Lee, Senior Scientist in the Health and Environmental Review Division of the EPA's Office of Toxic Substances, indicated that many of his best staff members are eagerly searching out the "private" sector job market. This forecast should be tempered by other factors (frustration with

bureaucratic functions, office environment, etc.) that influence career changes. The net result is the same. Less qualified scientists will be involved in formulating policy and managing technical programs leading to toxicology testing regulations.

Impact of Regulatory Changes on Toxicology Testing

Specificity/Uniformity of Regulations

Throughout the next decade a large number of new regulations and in-house regulatory agency policy changes will require standardization of toxicology testing protocols and procedures.

1. National and international coordination (formally through the Inter-agency Regulatory Liaison Group (IRLG) and the OECD) has identified toxicology needs that the regulatory agencies have in common and that are candidates for standardization. This can eliminate the conflicting policies and regulations that have been promulgated as the regulatory agencies implemented programs to satisfy the unique problems perceived by Congress when establishing their regulatory authority.

2. Uniform procedures for developing toxicology data can simplify and improve the efficiency of the regulatory decision-making process. Some criticize that this has a negative effect on technology advances and simply serve as an "institutionalized mechanism for saying 'no'" (Laubach, 1981).

There will be an increase in the number of regulations that specify which toxicology tests must be performed on specific chemicals.

1. New specific testing regulations will be most numerous from the EPA as Test Rules promulgated under TSCA.

2. The FDA and EPA (under FIFRA) have an established track record for requiring specific testing. These, however, will increase as technology advancements identify the importance of certain toxic effects data in developing safety standards and regulations.

3. With the regulatory agencies' (particularly the EPA and OSHA) focus on the "biggest" and "worst" problems with the greatest public health payoff, the toxicology testing performed will have to be extremely detailed and thorough to support the resulting "end-point" regulations, and be able to withstand the anticipated legal challenges to enforcement.

Self-Regulation

Self-regulation will have only a minor impact on reducing the number of specific toxicology testing regulations during the next decade. By and large, the existing regulations have not prompted an atmosphere of "self-regulation" on the part of industry. Many industries are establishing significant in-house

toxicology testing facilities/capabilities. Their motives for this, however, cannot be proven to represent voluntary compliance with the spirit of health and environmental legislation. It is generally felt that the current large investments being made by industry in toxicology represent their reaction to State and Federal regulations. Dr. Donald Barnes, Science Advisor to the EPA Assistant Administrator for Toxic Substances, indicated that as TSCA becomes accepted as part of the cost of doing business of the chemical industry, more and more companies will have to do toxicological testing. This does not represent a trend toward "self-regulation." It represents self-testing in response to a regulatory requirement.

Performance Responsibilities

No new regulations are anticipated during the next decade that would change the current Government versus "private" sector responsibilities for performing toxicology testing. However, some political and legal pressures from regulatory agencies will increase the amount of "private" sector testing over and above that required by existing Congressional authority.

There are only a limited number of Public Laws that specifically require toxicology testing to be performed by the "private" sector. The FDA and the EPA (under FIFRA and TSCA) are the most important in this regard. The testing requirements under TSCA require special emphasis because that Act is just being implemented by the EPA and the full toxicology testing workload has yet to be felt by industry. During 1981 and beyond, a large number of Test Rules will be issued by the EPA under TSCA to require industry testing of priority chemicals nominated by the Interagency Testing Committee (ITC). This testing, combined with that required to meet TSCA requirements for new chemicals (or chemicals to be used for a significant new use), will generate an escalating demand by industry to perform toxicology testing throughout the first half of the decade. Dr. Donald Barnes, Science Advisor to the EPA Assistant Administrator for Toxic Substances, felt that if TSCA were carried out to the letter, all the skilled resources in the nation would be required to support just that Act.

Toxicology testing in support of other regulatory requirements is largely the responsibility of the regulatory agency through its in-house R&D program. Their ability to satisfy the present and forecasted workload, however, has been and will continue to be doubtful in light of constrained Federal funding. According to Dr. Frode Ulvedal, 96 persons (approximately one-third) of the health effects staff in the EPA's Headquarters, Office of Research and Development will have to be cut due to the FY81 budget cuts alone (Ulvedal, 1981). The impact of future belt tightening will increase the desire by regulatory agency staffers to have "private" sector organizations perform additional toxicology testing. While such testing by the "private" sector is not specifically authorized, there are two documented examples to indicate that this is an ongoing and successful strategy for obtaining toxicology data for potential regulatory purposes:

1. The first example is the upcoming Scoping Workshop to discuss the EPA's strategy and response to the ITC Seventh Report in which two specific chemicals and two chemical groups were added to the list of

chemicals for priorty action by the EPA under TSCA. The Scoping Workshop is intended to bring together representatives from government, industry and the technical community in a nonadversarial environment to discuss openly and candidly the appropriate actions the EPA should follow for these newly nominated chemicals. One of the tentative agenda items for that conference will be to discuss "voluntary" testing by industry. It has been recently learned that one of the specific chemicals has been dropped from the Workshop Agenda because an informal agreement was reached with the affected industry to perform voluntary testing.

2. The pressures for transferring performance responsibilities to the "private" sector has been even more direct. Through the identification and evaluation of toxic and hazardous material disposal sites, industry has been required (through litigation) to develop adequate cleanup plans. Both the Hooker Chemical Company's involvement at Love Canal and the U.S. Army's experience at Rocky Mountain Arsenal represent recent examples where this has taken place. An "adequate" cleanup plan requires a definition of the safe or acceptable residual contamination level following the restoration effort. This forces the "private" sector to evaluate the toxic properties of the specific contaminants and possibly, to support toxicology testing. This testing would be performed to either define the necessary level of cleanup or refute an "unreasonable" cleanup level specified by the State or Federal regulatory agency.

Jurisdictional Aspects

Jurisdiction over toxicology testing regulations and requirements will remain largely at the Federal level for the next decade. This will occur in spite of the new political mood that favors a return of much regulatory authority to the States.

As the chemical age has grown, the environmental and occupational health protection responsibilities for our citizens has moved from State governments to the Federal government. A number of statutes are shared between Federal and State authorities and stipulate "whichever is the most stringent," with respect to standard setting. Although a number of statutes authorize State implementation of Federal standards and permit programs, Federal oversight and veto power remains. The Federal government is clearly responsible for developing the toxicology data for national standards which a State must then implement and enforce. Some States use their own toxicological testing resources for emergency and other priority health situations of particular interest (e.g., the State of New York evaluation of the toxic effects of contaminants in the Love Canal area).

Laws dealing with the registration of pesticides (FIFRA) and foods and drugs (FFDCA) are unlikely to be amended to transfer authority to the State level. Any activity which is interstate in nature and provides services to the Nation as a whole could not be easily decentralized from the Federal government. State authority to evaluate health risk and establish standards for environmental contamination (a more local concern) is conceivable and has taken place. The

States' active role in formulating more stringent compliance regulations (than the Federal regulations) does not mean States will necessarily require more toxicology testing. This usually means that the States will interpret the available toxicology data differently to account for local unique circumstances.

Health Hazard Decision-Making

There will be a significant number of regulatory and policy changes at all levels of Government (Federal, State and local) and in the "private" sector to require greater weight to economics and other societal concerns during health hazard decision-making. The impact of this will be attempts to develop more standardized "decision rules," using more quantified inputs during risk-benefit analyses. This may make regulatory agency decision-making more predictable and, thus, modify the "wait and see" approach industry usually takes with regard to self-regulation. The rate of progress and success in developing universally acceptable "decision rules," however, is debatable as many special interests will be quick to raise arguments for their unique situations.

Within Congress and the Executive Branch, laws already on the books will be reviewed as regulations affecting future deadlines (e.g., 1983 requirements in the Clean Water Act) are reviewed. These compliance requirements will be moderated during these reviews to take into account the prevailing economic, energy and other factors (Cywin, 1981). Accommodating these competing factors, however, will also permit the collection of better, more definitive health effects data for the eventual compliance regulations. Thus, these roll backs should have either a static, or possibly increasing, effect on the amount of toxicology data that will need to be generated during the next decade. Moderation of some regulations is taking place in recognition that the basic statutes are (1) overly demanding and technically complex, (2) economic and/or energy intensive in their consequences, (3) sometimes conflicting with each other and (4) at times, seemingly being implemented with an insufficient data base. Therefore, the absence of a sufficient data base is one of the reasons for these roll backs. This will probably generate requirements to produce more and better toxicology data.

Decision-making within the regulatory agencies themselves will, of course, be influenced by the appointees designated to the critical management positions. The Reagan Administration's desire to more fully consider economics and the States' rights in the regulatory arena has already been discussed. The chemical industry has a much more sympathetic representative with President Reagan, and is reported to have a strong influence in the selection of people to fill many sub-Cabinet regulatory positions, especially in the EPA (Sinclair, 1981).

Health hazard decision-making will continue to be challenged by public and industrial groups through court actions. A recent example of this was the unsuccessful attempt by OSHA to establish a more stringent occupational workplace standard for benzene (Supreme Court, 1980). The industrial effort was successful here because the court demanded proof that the lower workplace standard was necessary to protect human health. Although a large and somewhat conclusive data base exists linking benzene with leukemia, the court was not convinced that the relationship was sufficiently established, especially for the recommended lower concentration, to require a regulatory change. This further supports the requirement for comprehensive toxicology data base development to support regulatory decision-making.

A long-term (beyond 1985) change in health hazard decision-making will be seen when the generation of persons who grew up with an environmental "education," starting in high school and college, begin moving into the decision-making fabric of industry and government. This generation will take many years to replace the older decision-makers but should eventually help reduce the adversarial roles between industry and Government with regard to health hazard regulations and standard setting (Cywin, 1980).

A somewhat analogous example of this new decision making process can be seen in the automobile industry where union representatives have been given seats on the Boards of Directors. This is out of line with the traditional adversarial role between unions and management. The perspective gained, however, may be responsible for the recent union membership approvals of pay cuts in order to save their jobs.

In this same atmosphere, high ranking industry officials may eventually be permitted to participate actively in the decision-making processes of Federal regulatory agencies. Under present rules and regulations, they have input through "public comment" provisions, but do not participate in the decision-making itself. Direct communication, at the time of decision making could lead to more productive decisions as well as more voluntary testing by industry.

Toxicology Testing Workload

The overwhelming impact of the forecasted regulatory changes will be to require more toxicology testing of chemicals, more testing per chemical, and more repeat testing to confirm inadequate or conflicting findings. It should be recognized that this impact is not restricted to the U.S. Other industrial nations are developing similar toxicology testing needs. The OECD has been developing a set of guidelines for its member nations to follow in order to facilitate the safe commerce of chemicals (OECD, 1979; 1980). The OECD anticipates reaching an agreement regarding testing guidelines during the spring of 1981. Such cooperation reflects the international priority for performing toxicology testing.

According to Dr. Richard Hill, Science Advisor in the EPA's Office of Pesticides and Toxic Substances, there is only a world-wide capability for about 500 reliable, long-term bioassay test programs per year (Hill, 1981). Dr. Hill estimates that there is an unrequested need to at least double that capability during the next decade. The only major threat to his estimate would be major downgrading or repeal of the present legislation, which is unlikely. The principal factors supporting this increased workload forecast are as follows:

1. The U.S. has established basic statutes, covering just about every conceivable exposure route, to protect the public from toxic chemicals in the workplace, marketplace and the environment. Public support for the basic goals of these statutes is high. Although the new Administration and economic factors may result in a slowdown of new regulations and a roll-back on some others, it should be recognized that we start 1981 with a large backlog of toxicology testing needs. This backlog has been established largely in response to the requirements for "private" sector testing under TSCA, FIFRA and FDA. A

backlog in Government sponsored toxicology testing also exists. This consists of testing to support the development of health standards and to validate or defend standards already on the books.

2. As mentioned above, there is general public support for the legislative items on the books. There are a number of success stories in which a cleaner environment or a more healthy workplace is recognized as having resulted from Federal legislation (Cywin, 1980). The new generation of people who grew up with an environmental education will resist any major changes in the existing legislation and health standards (Cywin, 1980). An assumption made for this report was that unions will continue to demand a healthy workplace. The validity of this assumption, however, may be questionable in light of recent union agreements to hold the line (and permit certain roll-backs) on salaries in order to forestall plant closings. Workers may, in fact, agree to relaxed workplace health standards if it means job retention. These, however, are potential changes in the "end-point," compliance regulations and do not necessarily impact the amount of toxicology testing required to permit decision-making.

3. The Reagan Administration is also likely to maintain and, possibly increase, toxicology testing requirements in spite of its policy toward over regulation. The over-regulated "backlash" would, on the surface, signal a slowdown in all new regulations. The Administration will no doubt attempt to be more deliberate in implementing future standards and regulations (Cannon, 1981; Hilts, 1981). This, however, requires more data and, thus, more toxicology testing to further define the health risks that will be more equitably balanced with the benefits. More data will be needed to establish whether or not "end-point" regulations are needed or to establish threshold limits for unacceptable health effects.

4. Just prior to the change in Administrations there was a rush of new health and environmental regulations (Hilts, 1981). Even under a Reagan Administration freeze on new regulations there would be no significant short-term decrease in the present toxicology testing workload. As discussed earlier, the workload due to full implementation of TSCA has not been felt by industry to date.

5. The existing state-of-the-art for toxicology testing is expensive and time-consuming but is all that is available for regulatory decision-making. In addition, the statutes were set up by the Congress as proper vehicles for litigation. Most standards or regulations that are set aside or remanded by the courts are generally thought of as having an inadequate data base. Hence, the need for still additional toxicology testing to support more defendable "end-point" regulations exists.

6. A final factor affecting the workload for toxicology testing involves international coordination and commerce. Other industrial nations are developing similar toxicology testing needs. The OECD has been developing a set of testing guidelines for its members to follow in

order to facilitate the safe commerce of chemicals. In the very long-term (10-20 years), this standardization may reflect a reduction of certain toxicology testing that otherwise would have to be performed in the U.S. The impact of this will be difficult to see because of the major backlog for toxicology testing that currently exists or will be forthcoming through the implementation of laws (TSCA) already on the books. Therefore, performance of testing by international organizations that also satisfies U.S. testing requirements is not anticipated to have a significant impact on the U.S. "private" sector workload within this decade.

Conclusions

Regulatory Impact on Army Toxicology Testing Requirements

Two assumptions are made to make it possible to identify the regulations that will directly affect the Army's toxicology testing requirements. The first is that the Army will strive to conform to Federal regulations wherever possible. The second assumption is that the Army will be responsible only for toxicology testing related to Army-specific substances, or substances that are used in Army-specific uses that differ significantly from other uses. The Army will not be responsible for performing toxicology testing on the commercially available substances it uses, or for substances used in applications encountered elsewhere in commerce.

Federal Acts that have the potential for imposing toxicology testing requirements on the "private" sector are summarized in Table 8. These Acts are the FFDCA, TSCA, the Pesticide Act and the Consumer Product Safety Act. Based on the above assumptions, the Army would be responsible for toxicology testing of any Army-specific substance or Army-specific use, if one of those Acts required testing for that substance or use.

Since the section of the Consumer Product Safety Act that can require toxicology testing so far has not been used, it is unlikely that it will impact measurably the Army's toxicology resource requirements.

It is also unlikely that the Army will be required to do a significant amount of toxicology testing in response to the Pesticide Act. The Army can be expected to normally utilize commercially available pesticides; therefore, the producers of the pesticides will be responsible for performing any required testing.

The FFDCA and TSCA are the regulations projected to have the major impact on the Army's toxicology testing requirements. The FFDCA establishes regulatory requirements on food additives, drugs, veterinary medicines and cosmetic substances. The TSCA has the potential of requiring the Army to perform toxicology testing of all Army-specific chemicals and other chemicals used for Army-specific uses, if they are significantly different from uses that are not Army-specific.

While enforcement of the FFDCA is anticipated to be unchanged in the future, the effect of this Act upon the Army's toxicology resource requirements will be smaller than the potential impact of TSCA because the scope of FFDCA is so much smaller than that of TSCA. However, those sections of TSCA relating to requiring toxicology data on existing chemicals has not been fully implemented.

TABLE 8 REGULATORY ACTS THAT POTENTIALLY AFFECT THE ARMY'S TOXICOLOGY TESTING REQUIREMENTS

Act	Context of Impact on Army	Enforceable Aspects	Projected Enforcement
1. FFDCA	Toxicology Data required to prove safety of Army-specific: a. Food Additives b. Drugs c. Veterinary Medicines d. Cosmetics	Data must be submitted prior to clearance of substance by the FDA	No change in present enforcement projected
2. TSCA	Toxicology Testing required for use of Army-specific: a. New chemicals b. Existing chemicals in new uses (Army-specific) c. Existing chemicals (first priority on potentially hazardous chemicals)	1. EPA can require toxicology data on: a. New chemicals b. Existing chemicals in significant new uses c. Existing chemicals in use 2. EPA can specify method (used to obtain data)	Toxicology data required for: a. New chemicals b. Existing chemicals in significant new uses c. Existing chemicals selected by ITC, if insufficient data exists for assessment
3. Pesticide Act	Toxicology Testing required for Army-specific pesticides	Test data can be required for existing and new substances	Limited enforcement, especially for existing substances
4. Consumer Product Safety Act	Potential exists for toxicology testing requirements for Army-specific chemicals	Toxicology data can be required to prove chemicals specified by CPSC are not carcinogenic or toxic	Relevant section of Act has not used and is not projected to be used

It is concluded that the enforcement of TSCA will center upon the requirement for toxicology data on new chemicals or significant new uses of existing chemicals in significant new uses, if the EPA determines that they may constitute an unreasonable risk to health or the environment. The EPA, under TSCA, will also require toxicology data to be submitted on existing chemicals if they are nominated by the ITC for an EPA health or environmental hazardous assessment, when insufficient data on the chemical for the assessment exists.

The Army's toxicology testing resources also will be indirectly affected by regulations and legal pressures stemming from regulatory agencies. The next section addresses these factors.

Regulatory Changes

A summary of the major regulatory changes that are likely to take place during the next decade to impact toxicology testing is provided in Table 9. Included in the table are brief statements for the basis (reason/purpose) for the forecasted change and the specific impact the change will have on toxicology testing. No specific time estimates are provided for these forecasted changes. The changes will occur continually as new regulations are promulgated by the individual regulatory agencies as each adopts the change through reorganization or more complete implementation of their respective programs. The toxicology program manager should use Table 5, "Indicators or 'Flags' of Federal Regulatory Changes," to formulate specific time estimates for regulatory changes of special interest.

The analysis of regulatory agency changes has led to a consistent finding that major increases will be required in all resource categories to meet future regulatory requirements for toxicology testing. Disregarding the significant impact of inflation, the cost for performing toxicology testing will increase due to an increased number of compounds that will require evaluation and the greater amount of testing required per compound. Added to this are increased salary costs needed to attract and retain certain scarce personnel resources such as veterinary pathologists.

These increases will take place in spite of the forecast that no new major items of legislation involving toxicology testing will be enacted during the next decade. It is believed that the existing Federal legislation (much of which was enacted during the 1970's) established requirements for health standards and regulations for nearly all human exposure scenerios of significant concern. The regulations already on the books or proposed (to be promulgated during 1981-1982), establish an immense backlog of toxicological testing that will not be dealt with rapidly where Federal regulatory agency R&D funds must be used, but will require major investments where the responsiblity for testing rests upon the "private" sector.

Legislative activities during the 1980's will be restricted to the review of the existing laws. The over-regulation "backlash," to slow down or stop new regulations and to rollback existing regulations will be successful during the Reagan Administration in both this legislative review process and through influencing decision-making on specific health standards and compliance deadlines within the regulatory agencies. This, however, is not anticipated to diminish the requirements for toxicology data. It is the cost of pollution control, banning of existing products in the marketplace, etc. that is of

TABLE 9 SUMMARY OF FORECASTED REGULATORY CHANGES THAT MAY IMPACT TOXICOLOGY TESTING

Regulatory Change Will Require:	Reason/Purpose	Impact on Toxicology Testing
1. Greater number of chemicals for toxicology testing by "private" sector	a. Full implementation of TSCA b. Continued "public" concern for additional toxic chemical hazards c. Continued industry pressures to refute regulatory compliance requirements d. Constraints on Government funding for toxicology testing	a. Increase world-wide demand/competition for toxicology testing facilities and trained professionals b. Maximum use of regulatory authority for "private" sector toxicology testing
2. Greater number of toxicology tests per chemical	a. Technology advancements identify importance of specific toxic effects b. New test methods gain acceptance (*validated*) for use in regulatory decision-making c. Use of nonanimal screening tests for establishing priorities for further animal testing d. Requirement for data on all significant effects for comprehensive risk-benefit analyses	a. Increased requirement for facilities and personnel for screening and special toxicology studies b. Increased overall requirement for toxicology testing resources c. Increased adherence to detailed, standard protocols and procedures d. Increased requirement to establish threshold levels for specific toxic effects e. Long-term animal studies will continue to be required as the principal basis for regulatory decision-making
3. Adherence to "standard" or "universal" testing protocols and procedures	a. Simplify and standardize use of toxicology data in regulatory decision-making process b. Establish baseline for measuring quality of toxicology data	a. Toxicology data base will satisfy requirements of several regulatory agencies where applicable b. Continued applicability for adherence to Good Laboratory

continued-

Table 9 - continued

Regulatory Change Will Require:	Reason/Purpose	Impact on Toxicology Testing
	c. Interagency and international coordination and cooperation on toxic chemical hazard assessments d. Make maximum use of authority to require "private" sector testing to meet regulatory agency data base needs	Practices (GLP) c. Increased overall toxicology workload because universally acceptable protocols will be more comprehensive to meet unique requirements of all cooperating regulatory agencies d. Reduced innovation permitted during toxicology testing e. Federal regulatory agencies will continue to define the "acceptable" state-of-the-art for toxicology testing. f. Toxicology testing protocols will continue to be consolidated and expanded to cover all aspects of the hazard assessment process (including exposure assessments).
4. Slowdowns, rollbacks and/or deletions of health standards, control requirements and compliance deadlines.	a. Greater concern for economic impact of compliance b. Recognition of technical complexities/limitations to achieve regulatory goals and objectives. c. Return regulatory authority to States. d. Permit development of complete data base prior to promulgating regulations.	a. Will cause an increase on overall toxicology workload. Toxicology data will still be necessary to permit decision-making on specific health standards or the amount of residual risk that is "acceptable" if the no-effect level is not selected for the standard.

greater concern to industry than the cost associated with toxicology testing. The efforts to roll back or delete certain compliance regulations may, in fact, increase the demand for toxicology data because of the increasingly complex and detailed risk-benefit analyses that the "backlash" is demanding to effect more favorable (more balanced for economic considerations) decision-making.

Therefore, new regulations dealing with toxicology testing will be promulgated during the 1980's. Some will represent a relaxation of certain compliance requirements to bring health risk concerns more in balance with other issues, especially economics. These should not significantly impact overall toxicology testing requirements. This is because many other regulations will dictate additional toxicology research so that the more quantitative risk-benefit analyses can be performed. Still other regulations will be promulgated to standardize the manner in which toxicology evaluations are performed. Finally, regulations dealing with short-term, inexpensive screening tests will be promulgated throughout this period but, due to delays in their acceptance for predicting human health hazards, are not likely to have an impact on reducing the amount of testing per compound until very late in the decade.

The international proliferation of health standards and regulations, modeled after the U.S. examples, will add to a projected shortfall in toxicology resources (primarily skilled professionals) world-wide. Some relief in this world-wide competition for toxicology resources may be experienced in the long-term (1990 and beyond) as international coordination efforts, currently underway, mature so that the quality of toxicology data performed by the international community becomes more acceptable in the U.S. regulatory arena.

It is thus concluded that pressures from both the "health protection" and "regulatory backlash" sides will establish a demand for further toxicology testing. The 1980's will possibly be characterized as the decade for performance of the goals and objectives formulated during the 1970's. The 1980's should represent a period of intensive development of toxicology information to permit informed decision-making, resolve conflicts, and balance society's desire for a healthier environment with other conflicting factors.

Recommendations

The following recommendations are made to the manager of a toxicology testing program and reflect the impact that the forecasted regulatory changes will have on toxicology testing resources during the period from 1981 to 1990:

1. The capability (or identity of) available performers to conduct specialized toxicology tests not currently included in "standard" testing protocols should be established. Examples here include various animal and nonanimal screening tests and neurotoxic/behavioral effect studies. The program manager should monitor Federal Register publications of proposed Test STandards (under TSCA) as a "flag" for pending regulatory requirements to perform these specialized tests. Specialized tests are likely to be a sporadic requirement during the first half of the decade and become fully integrated into routine, standard testing protocols prior to 1990.

2. Advancements in toxicology testing technology should be monitored (through participation in professional society conferences, workshops, etc.) to provide an early warning of future specific regulatory changes impacting toxicology testing. With this early warning information, the program manager can then use the indicators or "flags" provided in Table 5 to formulate and refine time estimates for these potential changes.

In addition to the above recommendations, the following items are recommended for consideration by any manager of a toxicology testing program:

1. A significant increase (approximately twice the present level) in the demand for toxicology testing resources should be anticipated during the next decade. This increase is largely due to the pending full implementation of TSCA by the EPA. The demand will increase in all resource areas, i.e., trained personnel, equipment, laboratory space, animals, etc.

2. The most severe impact of this increased demand will be in the area of trained personnel. The lead time for trained and experienced personnel (approximately four years of graduate training) generally will be longer than for all other categories of resources (construction of new facilities, increased breeding capability for most animals, etc.). In addition, this is a resource that the program manager cannot easily control. Scholarship programs for key disciplines have been established with mixed results in other areas to meet this resource need.

3. This increased demand for toxicology testing resources will have an impact on all toxicology testing programs world-wide to include Government-supported laboratories and industry testing programs involved exclusively in new product (non-regulatory) developments. All program managers will be impacted by this general competition for the same resources.

4. A continued requirement (past 1990) should be anticipated to perform long-term animal studies in support of toxic compound human hazard assessments, especially where preliminary evidence of carcinogenicity exists.

5. Continued, possibly increased, emphasis should be anticipated on Federally mandated quality control and quality assurance procedures in performing all toxicology testing.

6. It should be anticipated that all regulatory agency toxicology protocols will become more "universal." Interagency (and international) coordination efforts will develop standardized testing protocols so that testing performed for one regulatory agency will be generally acceptable for other regulatory purposes.

7. The toxicology program manager should participate in the "public comment" process for proposed toxicology testing regulations. This is the only formal mechanism for the program manager to influence

such regulations. This may be especially critical when standardized or universal testing protocol regulations are proposed that require extensive testing for specific effects or by routes of exposure that are not always relevant. For example, a universal testing protocol may require testing by oral, inhalation and dermal routes of exposure. A specific chemical may be highly volatile so that inhalation would be the only significant exposure route of concern. Participation in the public comment process may be the most effective means to forestall such "unnecessary" blanket testing requirements.

8. Requirements should be anticipated to perform more extensive human exposure assessments to establish the priorities for performing toxicology testing. Regulatory agency requirements will emphasize human exposure assessment data particularly when reviewing recommendations to cease further toxicology testing on specific compounds.

IMPACT OF TECHNOLOGY CHANGES

New developments in the technology of toxicology testing result less because of regulatory requirements than as the result of work designed to fill data gaps and find methods of obtaining more data of better quality, using less time and resources.

The forecasts of technology changes described below were made from the perspectives of those toxicology subdisciplines that are considered important relative to the Army's needs. These subdisciplines are biostatistics, epidemiology, genetics, inhalation toxicology, neurotoxicology, oncology/biochemistry and general toxicology. An effort was made to project future technology changes in other areas, such as behavioral toxicology, which may have some effect on future resource requirements within the Army's toxicology testing program.

Basis for Forecasting Technology Changes

Predictions of future changes are based on the present state-of-the-art of toxicology testing, and a recognition of significant gaps in the toxicology data for which research to provide the missing information is underway.

State-of-the-Art

Table 10 summarizes the present state of toxicology technology. During the past 20 years, the basic toxicology requirements for compliance with regulations have undergone little change (Association of Food and Drug Officials of the United States, 1959; FDA, Unpublished guidelines for preclinical toxicity testing of investigational drugs for human use; FDA, 1977; FDA, 1979). It can therefore be concluded that basic tests required by regulations may not change too much during the next ten years. In addition, certain tests are so well established that changes in them within the next ten years are considered very unlikely:

1. The most baseline of all toxicology tests is the single exposure, acute toxicity test (LD_{50}), having a 14-day observation period. This is not expected to change, except when the researcher extends the observation period up to 30 days to obtain specific data.

TABLE 10 FACTORS IN PRESENT STATE OF TOXICOLOGY TESTING ON WHICH FORECASTS OF TECHNOLOGY CHANGE ARE BASED

1. Test Animals:

   a. Criteria for selection of species for testing:
      - Available data base for data correlation
      - Documentation of animal strain
      - Cost (of animal, facility to house animal and study that uses animal)
   b. Baseline animal for mammalian tests is mouse.
   c. Cost of animals sometimes dictates reuse of test animals (e.g., primates in behavorial toxicology screening tests).
   d. Standards for animal holding facilities:
      - American Association for Accreditation of Laboratory Animal Care (AAALAC)
      - American Association of Laboratory Animal Sciences for Animal Technicians and Caretakers (AALASATC)
      - National Institute of Health (NIH)
      - Good Laboratory Practices (GLP)

2. Test Protocols:[(a)]

   a. Acute toxicity test (LD_{50}) -- Single exposure followed by 14-day observation period.
   b. Subchronic Test -- 90 days of exposure with histopathology studies.
   c. Chronic Test -- 2 years of exposure, often using 2 species.
   d. Baseline number of doses in dose-response tests is 2 plus control.

3. Test Procedures:

   a. Testing for regulatory compliance requires use of GLP.
   b. Universities generally cannot meet GLP; therefore, not available for Government and industrial compliance testing.

(a) Minimum requirements for toxicology testing are LD_{50} and 90-day tests.

2. Subchronic (90-day) tests are not anticipated to be shortened.

3. Chronic (long-term or lifetime) tests are normally two years long. Recently, for carcinogenicity testing, the length has been decreased to one year. Further reductions in the length of the test are not expected during the next ten years (OECD, 1979).

Knowledge Gaps

Significant gaps in the existing toxicology data base are listed in Table 11. In the most general terms these are related to knowledge about: (1) differences in the ratio of uptake, excretion and metabolic transformation of specific chemicals, (2) the nature and rate of the chemicals metabolic transformation, if any, (3) the rate at which the chemical and its metabolites reach target organs, and the distribution of these chemical species among target organs, and (4) the nature of the reaction between the chemical and its metabolites and the target organ.

Elimination of data gaps in these areas would greatly facilitate interspecies correlations, and extrapolation of data from animal studies to determine acceptable human exposure levels. It would also be possible to replace many costly animal tests with short-term in vitro tests. Knowledge of the nature of the chemical and biochemical reactions occurring would simplify the projection of toxic effects, based on the structure of individual chemicals and groups of chemicals. Fewer tests would have to be performed since conclusions could be reached on the basis of tests using a few chemicals from each group.

While work is underway to fill these data gaps, they exist now and greatly increase the complexity and the amount of testing that is required. Unfortunately, the magnitude of these gaps is so large that they will not be eliminated within the next ten years.

Projected Toxicology Technology Changes

The following summarizes possible changes in the technology of toxicology associated with exposure assessments and studies of exposure routes, toxicology testing protocols, procedures and facilities, human studies, quality assurance applied to toxicology testing, and interpretation of toxicology data. Additional information on possible technology changes is available in the literature (Bar-Shalom et al., 1975).

Exposure Assessments/Exposure Routes

Table 12 is a summary of projected technology changes related to exposure assessments and exposure route studies. One significant change that may occur is the acceptance of the total dose concept for exposure assessments of hazardous chemicals, as has long been done for ionizing radiation.

Within the next ten years, risk assessments may be based on the results of comprehensive relative exposure assessments, in which the risk due to any source of exposure is calculated from the amount of exposure from that source, divided by the total exposure from all sources.

TABLE 11 SIGNIFICANT GAPS IN TOXICOLOGY DATA

Description	Activities Motivated by Gaps
1. Mechanism of toxic effects: a. Mechanism of initiators and promoter b. Realtionships between chemical structure and toxic effects c. Role of metabolites of hazardous chemicals	• Correlations between in vitro and in vivo tests • Characterization of effects of initiators and promoters • Studies of delayed sequela • Definition of structure-activity relations (SAR)
2. Interspecies correlations for relations between: a. Dose and response b. Route of exposure and response c. Chemical and target organ distribution	• Correlation studies between mammalian and submammalian tests for: - Screening tests - Tier approaches • Interspecies correlations to select animals that best simulate human response
3. Effects of age upon induction period and severity of toxic effects	• Studies of age-response and time-to-response versus age correlations
4. Subclinical effects, including behavioral changes, for many chemicals	• Tissue studies • Development of subclinical neurotoxicology screening tests • Behavioral tests
5. Cumulative exposure data on today's populations (for epidemiological studies)	• Establishment of the National Death Index (NDI) • Use of historical data related to Social Security Numbers attempted

TABLE 12 FORECASTED CHANGES IN EXPOSURE ASSESSMENTS AND ROUTES OF EXPOSURE

Change	Flag	Time Frame
1. Exposure Assessments:		
a. Acceptance of comprehensive relative exposure assessment Methods	Federal Register announcements on Rebuttable Presumptions Against Registration (RPAR).	1983-4
b. Application of Total Dose Concept to chemicals	Change Underway	1983-4 for wide-scale application for selected chemicals
c. Increased use of dosimetry	Change Underway	1981-on
2. Exposure Route Studies:		
a. More differential exposure route assessments	Change Underway	1980-on
b. Increased study of percutaneous route	Change Underway	1980-on
c. Increased study of toxicokinetics, pharmacokinetics and biotransformations	1. Use to detect carcinogenicity 2. Adoption by EPA 3. NTP studies	1983-on

A flag of imminent changes in this area is the EPA's Pesticides Program under FIFRA, which is the most advanced risk assessment regulatory process. Presently, risks due to genetic hazards are identified by obtaining positive results in mutagenic screening tests for two submammalian species. This is considered to be justification for a rebuttable presumption against registration (RPAR) (EPA, 1978).

Mutagenicity tests in genetic toxicology consist of:

1. Bacteriological tests
2. Tissue culture tests
3. In vivo insect (Drosophila melanogaster) tests
4. In vivo mammalian tests

The equipment for these tests has been established and probably will not change except for the use of radionuclides and stable tracers for dosimetry studies (Aaron and Lee, 1978; Lee, 1978). These studies permit detection of carcinogenicity for low to average carcinogens using fewer animals than the specific locus test, since detection of the tracer within the DNA of the exposed animal is a straightforward indication of the mutagenic property of the tagged chemical to which the animal was exposed.

In larger animals than mice (e.g., dogs), radionuclides and stable tracer techniques can be used to perform differential exposure route assessments, in which the distribution of the chemical among various target organs can be measured.

Recent studies have also placed greater emphasis on the percutaneous route of exposure for certain chemicals having neurotoxic effects. These studies, plus dosimetry studies, will increase in importance in the future. This demand will increase the need for professionals and technicians trained in toxicokinetics, pharmacokinetics, biotransformation (metabolism), and analytical chemistry (especially for use of tracer techniques).

Testing Protocols

Table 13 summarizes the predicted changes in toxicology testing protocols. During the next ten years, toxicology testing will make greater use of screening tests and tier approaches to testing, and more test data will be obtained during definitive tests. At least in the area of neurotoxicology, greater emphasis will be placed on 90-day tests during the next decade, with acute tests performed mainly as range-finding studies for 90-day and long-term tests. The importance of chronic tests, however, will also increase due to concern about the effects of lifetime human exposures, and the possible special vulnerability of people in old age. Recent breakthroughs in the classification of neurotoxic diseases, according to the cellular target site, will allow selection of neuropathological examinations to detect very early changes and the design of special behavioral, neurological and electrophysiological studies to detect these cellular changes.

Techniques are now being investigated to reduce the time and cost required for risk assessment procedures based on chronic tests and epidemiological studies. These are (Staffa and Mehlman, 1979; Infante and Legator, 1980; PHS, 1979; Goldberg, 1974):

TABLE 13 FORECASTED CHANGES IN TOXICOLOGY TESTING PROTOCOLS

Change	Flag	Time Frame
1. Screening Tests:		
a. Acceptance of short-term screening tests to detect hazardous substances	• Change underway through EPA's Pesticides Program under FIFRA	1980-on
b. Increased use of biological monitoring to detect subclinical effects	• Establishment of tissue bank by NTP	1980
2. Tier Approaches--Acceptance as part of present and future compliance protocols	1. Present FIFRA protocols 2. Acceptance of EPA mutagenicity testing guidelines	1980
3. Definitive Tests:		
a. Chronic tests' length reduced to 1 year	• OECD agreement with EPA	April, 1981
b. Increased number of:		
• Tests using aged animals	1. Peto's work on asbestos 2. National Institute on Aging budget increased 3. Reports from NTP Projects	1984-6
• Interspecies correlation studies for chronic tests	1. CIIT work on comparative metabolism 2. Science Advisory Panel discussion 3. Workshops, etc.	1986-91
• Studies of carcinogenic initiators and promoters	• Change underway	1981-on
• Mathematical models for chronic tests	• Present attempts to validate models in inhalation tests	Before 1991
c. Possible replacement for Draize Test Test	• Acceptance of CTFA work • Recent funding of Rockefeller study	1986-91

1. Mathematical models

2. NCTR ED_{01}

3. New short-term tests being investigated by the NTP:

   a. Microbial mutagenesis assays
   b. Mammalian cell transformations
   c. Immunology and neurobehavioral tests

4. Tests being investigated by NIOSH to assess reproductive hazards (in addition to epidemiology):

   a. In vivo prenatal and neonatal exposures
   b. In vitro teratogenesis test systems using organ and whole embryo culture (rather than single cells) and metabolic activation procedures.

Mathematical Models. Emphasis in math models will probably shift from simple models, such as straight-line extrapolations, one-hit and Mantel-Bryan procedures, to multistage and multi-hit models. In the past three years, the multi-hit and Armitage-Doll multistage models have received much attention. These techniques require more data to be obtained per test than the simple models, because the newer models require time-to-tumor data (serial sacrifice) and data at more dose levels than the older models (IRLG, 1970; Van Ryzin, 1980; Fiserova-Begerova, 1976; NAS, 1977; Staffa and Mehlman, 1979; Ramsey, et al., 1979). *Therefore, increased use of math models will increase the number of animals needed for tests and the workload of the technical staff. They will also necessitate the use of computerized treatment and storage of the larger volume of data obtained.*

This shift toward obtaining more data during a testing program is also shown in a report by a recent scientific committee on the Food Safety Council (Food Safety Council, 1980). This detailed an ideal system of tests that would be performed when possible. Highlights are more metabolic and genetic testing at subchronic levels, more extensive chronic tests with five doses or more, and serial sacrificing to obtain time-to-response and time-to-tumor data.

Screening Tests. Other efforts are underway to develop short-term screening tests, primarily to be used to prioritize testing of potentially hazardous substances. Screening tests could be used to ensure that limited resources are spent on assessments of the chemicals determined on the basis of screening to be the most hazardous (Kraybill and Mehlman, 1977; NAS, 1977; Infante and Legator, 1980; NAS, 1975; Hodgson, Bend and Philpot, 1980; Berkey and Sherrod, 1977; Reeves, 1981). For example, The Interagency Testing Committee (ITC) is investigating tests that use Hydra to screen for potential teratological effects.

There is potential for future replacement of at least some animal tests by short-term screening tests. For example, within the EPA's Gene-Tox Program, good correlation has been shown between sex-linked recessive lethal tests in Drosophila melanogaster and carcinogenic tests for somatic cells in mammals.

Mutagenicity screening tests also are used in the EPA's Pesticides Program under FIFRA as support for a rebuttable presumption against registration. Programs funded by CIIT are attempting to develop other short-term tests to be used as replacements utilizing human tissues for animal studies.

Tier Approaches. Tier approaches to organizing toxicology testing programs have been developed, like screening tests, to most effectively use testing resources and to prioritize the specific tests to be performed. Past tier approaches consisted of:

1. Structure-activity relationships (SAR) studies (Arrhenius, 1974).
2. Short-term assays
3. Animal bioassays
4. Epidemiology studies

Now the limitations of this approach are recognized. Animal bioassays are costly and take time. Epidemiology studies are also costly and take time, but in addition, often are not possible due to the lack of acceptable study populations. Therefore, structure-activity studies and short-term assays have taken on greater importance in the tier approaches, especially within regulatory agencies that have urgent needs to rapidly arrive at rationale for decision-making. Today, however, SAR studies are limited by the lack of data on chemicals other than organophosphorus compounds. Also, certain chemicals are now known to be indirect carcinogens in that it is the metabolites of the chemicals that produce tumors. Until the chemistry and biochemistry of the biotransformation of these chemicals are evaluated, use of SAR for them may not be productive.

Definitive Tests. Protocols for definitive tests are undergoing review with the objective of establishing unified guidelines (IRLG, 1979). Typically, these studies recommend obtaining the time-to-response data at four or five dose levels discussed above in relation to math modeling. This larger quantity of data is considered essential for accurate statistical treatment of the data (Food Safety Council, 1980).

As chemical and biochemical data increase, particularly in areas of metabolic pathways, pharmacokinetics, homeostasis of mammalian systems, genetics and cellular membrane structure and formation (including cell molecular targets involved in sustaining bodily functions), emphasis may shift to hazard assessments of groups of chemicals rather than tests of individual compounds (Kraybill and Mehlman, 1977; NAS, 1977; PHS, 1979; Hodgson, Bend and Philpot, 1980; Reeves, 1981; Arcos, Argus and Wolf, 1968; and Lee, 1977). This will tend to shift some testing requirements toward more *in vitro* studies, and will eliminate more repetitive testing.

Consolidation of protocols is considered to be an unlikely change within the next ten years because of the investment that is made in each test. The possibility of confusing test results because of use of multiple procedures during a single test appears at this time to incur an unjustified risk. However, there will be the development of new protocols to evaluate recently recognized effects. New tests will be performed using aged animals (12 to 18 months old at the start of tests using rats) to determine the effects of age on time-to-response and susceptability to response. Also, some chemicals have

been found to be initiators or promoters of carcinogenicity, although they themselves are not carcinogenic. Although synergistic effects are not considered to be important subjects for testing during the next ten years, because of the low exposure normally encountered by humans, studies of initiators/promoters will increase. They may be used to shorten the length of chronic carcinogenic tests, but they will also prompt additional tests of chemicals to ensure that they do not facilitate carcinogenic responses to other chemicals in the environment.

Use of radionuclides in carcinogenic testing will play a role in improving the extrapolation of animal data to man. This will be due to the fact that detection of alkylation of DNA by tagged chemicals can be detected at lower dose levels than normally required in animal tests. Since lower doses can be used, doses more closely similar to human exposures can be used and data extrapolation will be simplified. Another significant change in carcinogenetic testing has been the recent reduction in the length of the tests from two years to one year. This has occurred through a cooperative agreement between the OECD and the EPA. Resource requirements will be significantly reduced, on a per test basis, because of this change.

Neurotoxicology and behavioral toxicology are not as accepted as are the carcinogenicity and mutagenicity technologies. However, neurotoxicology has made significant technological advances during the 1970's, resulting in new approaches to assay compounds for chronic neurological effects (Spencer and Schaumburg, 1980). Wide acceptance of these techniques is limited by the limited number of personnel capable of performing the assays.

The best of the validated approaches involves examination of selected areas of the nervous system (brain, spinal cord or peripheral nerves) for pathological changes using contemporary morphological methods.

Other tests being developed rapidly are organotypic tissue cultures and functionally coupled explants of spinal cord, dorsal root ganglis and striated muscle. The ITC has recommended to the Office of Management and Budget (OMB) that this technique should receive added funding. The petrochemical industry is also interested in this technique as a method of reducing animal testing costs.

Other tests using reconstructed and dissociated tissues have not yet been validated. Nerve conduction tests are promising as screening methods (which may be in use by the year 2020) but are restricted to chemicals that affect the peripheral nervous system.

Behavioral toxicology suffers from a lack of specificity and will require a larger data base before it is validated and widely accepted. However, interest within the FDA, EPA and NIOSH will encourage additional research (NAS, 1977; Infante and Legator, 1980; PHS, 1970; NAS, 1975; Lee, 1977; and Ekel and Teichner, 1976). As a result of these efforts, behavioral screening tests may be developed within the next five years.

The Draize Test for cutaneous and ocular irritation may be replaced within the next three to five years by a new procedure. This will result from efforts by the cosmetic industry to reduce testing costs.

Testing Procedures

Forecasted changes in testing procedures are summarized in Table 14. More animal species will be used in testing (Kraybill and Mehlman, 1977; NAS, 1977; PHS, 1979; NAS, 1975; NAS, no date; Malins and Jensen, 1981; and Calabrese, 1978). These may include aquatic and avian forms (chickens for organophosphorous neurotoxicity studies) and smaller forms of primates (e.g., marmosets and lemurs) to supplement more costly Rhesus and Cynomolgus monkeys. Rodents will continue in high use.

Other changes in animal testing require the use of more animals per test. Concerns for greater statistical validity in controls obtained from animals receiving the lowest dose (since usually the lowest dose is higher than human exposure) will require as much as twice the normal number of animals today. There will be less reuse of animals in the future, except for limited reuse of primates. Certain tests will be required to use both positive and negative controls. Some studies may require vehicle, solvent and naive controls. Also, test procedures may involve the use of more dose levels than the present baseline (as discussed above). Instead of two doses plus controls, certain requirements will be generated for as many as four or five doses plus controls. Serial sacrificing of animals will also increase animal requirements.

While concerns about the statistical value of test data generate requirements for more test animals, concerns about unintentional exposure of animals, especially during chronic tests, to pollutants contained in feed, drinking water and even air, will generate incorporation of more purity checks. This will require additional analytical chemistry testing. Toxicology testing facilities also may be modified to incorporate purification systems (ion exchange, carbon adsorption, and UV radiation) to purify drinking water. Animal feeds may be checked by an analytical facility within the toxicology testing facility, or by purchasing high purity feeds at higher cost. Air quality presently is of lower concern, except for behavioral studies. Therefore, wide-scale incorporation of improved ventilation and air filtration systems are anticipated to lag behind the use of more pure drinking water and feed.

Tissue culture assay methods will be introduced slowly over the next 20 years if their reliability and reproducibility are demonstrated within the next five years. Neurotoxicity tests using tissue samples from the nervous system have recently undergone a significant advancement through the use of fixation and epoxy embedding techniques with light microscopes for histological studies. This increases the resolution of the light microscope beyond that otherwise possible. The tissue preparation still requires the use of equipment now used to prepare samples for electron microscopy (heavy-duty microtomes, knifebreakers, automatic tissue processors, perfusion pumps), but binocular, bright-field light microscopies (double-headed in some cases for team viewing) can be used instead of the more costly electron microscopes required in the conventional procedure.

TABLE 14 FORECASTED CHANGES IN TOXICOLOGY TESTING PROCEDURES

Change	Flag	Time Frame
1. Types and Use of Animals:		
a. More species of test animals:		
• Hogs and minipigs for cardiovascular and digestive system studies	• Change Underway	1981-91
• Primates for subclinical and behavioral studies	• Change Underway	1981-91
• Other species for studies of specific organs	1. CIIT work on comparative metabolism 2. Science Advisory Panel discussions 3. Conferences and workshops	1986-91
b. Decreasing reliance on mouse as baseline mammal	• Federal Register protocols that do not specify species	1986-91
c. Decreasing reuse of animals, except for limited reuse of primates	• Change Underway	1981-on
d. Use of cloned animals for tests	1. Work in other countries on mammals and primates 2. Start of work in U.S.	1991-2011
2. Numbers of Animals per Test:		
a. Increased numbers of controls: • Positive controls (vehicle/solvent/ naive controls) • Negative controls	• FIFRA requirements	1980-on
b. Increased numbers of animals exposed to lowest dose	• FIFRA requirements	1980-on
c. Serial sacrifice	• Acceptance of new math models	1981-on

continued-

Table 14 - continued

Change	Flag	Time Frame
d. Increased number of dose levels	• Acceptance of new math model and statistical treatments	1981-on
3. Routes of Exposure:		
a. Better control of testing environment: o Purity of food o Purity of water o Quality of air	• Change Underway	1980-on
b. Possible substitution of inhalation exposures in some long-term tests by less costly exposure methods	1. Journal articles 2. Conferences and workshops	1991-on
4. Number of Dose Levels (Use of 4-5 doses plus controls)	• Regulations and guidelines	1981-on
5. Data Evaluation:		
a. Increased data collection during tests	1. Use of new math models 2. Time-to-response data 3. Time-to-tumor data	1981-on
b. Increased use of computers for efficient data storage	• Change Underway	1981-on
c. Increased use of on-line data bases for assistance in data interpretation	1. EMIC and TOXLINE now 2. CSIN in future 3. QUASAR and PROPHET for SAR	1980-on
d. Establishment of criteria for negative decision for in vivo germ cell mutagenesis studies	• EPA Gene-Tox Program reports	1981-82
e. Use of light microscopy for histopathological assessment of tissues	• Journal articles	1981-84

Toxicology Testing Facilities

Table 15 provides a list of significant technology changes related to the facilities required for toxicology testing. In general, future developments will tend to provide greater protection to the animals, testing personnel and environment around the testing facility. Concerns about the exposure of animals to contaminants in drinking water, food and air, especially during chronic studies, provides the motivation to provide increased analytical capabilities to test for water and food purity, and to incorporate within the testing facilities equipment for purification of drinking water. Also, tissue studies require ultrapure (carbon adsorption and filtration) water and sterile hoods.

The general analytical techniques that will be required to support toxicology testing are:

1. High-pressure liquid chromatography (HPLC).
2. Gas chromatography (GC).
3. Gas chromatography/mass spectrometry (GC/MS).
4. Electron impact and chemical ionization mass spectrometry.
5. Nuclear magnetic resonance (NMR) spectrometry.
6. Infrared (IR), visible and ultraviolet (UV) spectrometry.
7. Wet chemical analyses.

Analytical support for routine analyses (expecially tests of food and water purity) will be done using an in-house, "core" analytical group. However, less frequent and more sophisticated analyses (GC/MS and NMR) may be most cost-effectively done by outside service organizations.

Unknown substances undergoing testing now tend to be considered hazardous until proven otherwise. In addition, unionization of animal handlers has occurred in some locations. Both factors lead to greater use of protective clothing and ventilation systems to protect workers from contamination and off-gassing from animals and inhalation chambers.

The maintenance of areas, designated as "clean" or "dirty", within the testing facility has been criticized in light of the tendency of workers to disregard the steps necessary to maintain the cleanliness of the areas designated as "clean". It will be necessary either to incorporate more extensive human engineering considerations to ensure the maintenance of the clean conditions, or eliminate the "clean/dirty" concept from future facilities to reduce their cost.

The major change in toxicology testing facilities will be the greater incorporation of equipment to safely dispose of solid and liquid wastes, including cage wash water, bedding material, carcasses, potentially hazardous chemicals, etc. For example, incineration of materials containing polychlorinated biphenyls (PCB's) must conform to disposal regulations that require incineration at high temperatures (1300 C for two seconds). Discharge of wastewater from toxicology facilities must also conform to either local regulations for discharges into sewer lines or federal regulations for discharge into the environment. The trend of controlling pollution at its source may in the future require toxicology facilities to provide some sort of wastewater treatment system, even if it now is tied to a municipal sewage treatment facility.

TABLE 15 FORECASTED CHANGES IN TOXICOLOGY TESTING FACILITIES

Change	Flag	Time Frame
1. Animal Holding Facilities:		
a. Increased use of high purity feeds	• Commerical availability of high-purity feeds	1981-on
b. Improvements in ventilation, cleanliness	• Few flags because of low impact of technology	
2. Worker Protection:		
a. Increases in use of protective clothing to: • Deal with unknown substances--now considered hazardous until proved otherwise • Protect against off-gassing from inhalation chambers and animals removed from them	1. Unionization of animal handlers 2. Compliance with NIH, GLP, Animal Welfare regulations	1981-on
b. Better ventilation (especially in necropsy labs) to reduce expose to formaldehyde	• Recent classification of formaldehyde as potential carcinogen	1981-on
3. Inhalation Chamber Design--More use of modularized chambers for exposure and holding	• Design of testing facilities	1980-on
4. Chemical Support:		
a. Increased analytical quality control: • Analysis of Feeds • Drinking Water analysis	1. Journal articles 2. Workshops 3. Federal Register guidelines	1981-on

continued-

Table 15 - continued

Change	Flag	Time Frame
b. Core Analytical facilities for frequent analyses, use of outside labs for sophisticated analyses (e.g., GS/MS)	• Workshops and articles on role of GC/MS, etc., in toxicology testing	1980-on
c. Increased emphasis on radionuclide and stable tracer measurements	1. Differential exposure route assessments 2. Dosimetry use in mutagenic studies	1980-on
5. Overall Facilities Design:		
a. Solid wastes disposal techniques (incineration) will be upgraded to comply with regulations (e.g., destruction of PCB's)	1. Incineration regulations 2. RCRA	1980-on
b. Wastewater may be treated before discharge from testing facility	1. Clean Water Act regulations 2. Local discharge regulations	1982-on
c. Incorporation of drinking water purification equipment (ion exchange, carbon adsorption and UV radiation)	1. Current interest, especially in Europe 2. Articles, conferences and workshops 3. Federal Register guidelines	1981-on
d. Change in treatment of "clean" and "dirty" areas of facilities, either: • Elimination of distinction due to disregard of requirements by employees, or • Incorporation of better human engineering	• Design of future toxicology testing facilities	1981-on

continued-

Table 15 - continued

Change	Flag	Time Frame
e. Incorporation of on-line information search facilities	1. Development of more and larger toxicology bases (EMIC, TOXLINE, CSIN, etc.) 2. Development of speciality data bases	1980-on

Recent designs of inhalation chambers have departed from the previous free-standing chamber concept. The most modern toxicology facilities utilize room-sized, modularized inhalation chambers integrated into the building. These chambers are utilized to hold the animals after exposure, or are attached to a conveniently accessible holding area immediately adjacent to the chamber. The advantage of this concept is that less labor is consumed during and after exposure because it is unnecessary to transfer animals from their cages.

Future toxicology facilities will make greater use of information acquisition and computerized data storage systems. Computerized systems will be required to effectively treat the increased amount of data required for statistical treatment of data, and to perform assessments using the sophisticated new mathematical models (NAS, 1977; Staffa and Mehlman, 1979). Tables are being developed with the Gene-Tox Program of the EPA for determining the size of a test necessary for a negative decision. Therefore, computer facilities will be used in some cases for planning tests as well as interpreting the results.

Similar equipment, or some of the same equipment, will be required to access on-line data bases such as EMIC and TOXLINE. These will become increasingly important as toxicology data becomes centralized (for example in the CSIN data base), and as data bases for SAR studies, such as QUASAR and PROPHET, are expanded. Appendix 1 further identifies the data bases referred to above.

The computer facilities will be staffed by programmers and math modelers, while the on-line search facilities are tended by technical information specialists and librarians. The workload of busy toxicology professionals will be reduced by use of information specialists and librarians to obtain special information and to routinely survey new issues of journals to provide the professional with the current articles in his or her research area.

In some cases, toxicology facilities may also include long-term animal tissue storage facilities to be used as references to human effects for persons who have been exposed to chemicals accidentally, through training or as part of research projects. Tissue samples such as blood, urine and feces may be of value in subclinical analyses of possible hazardous exposures.

Human Studies

Projected changes in the technology associated with human studies are summarized in Table 16. Data associating environmental agents to human cancer have been increasing exponentially with time (Maclure and McMahon, 1980). Funding for epidemiology research and training also increased during the same period. Funding has now leveled off, so further increases in data are not expected at the same rate.

Epidemiological studies may not always be considered as necessary verifications of animal tests, but will be used in applications not now associated with animal bioassay programs. For example, epidemiology may play a role in studies of occupational carcinogenesis, cancer risk assessment studies, teratogenesis and mutagenesis studies, and development or denial of biological response thresholds (Kraybill and Mehlman, 1977; NAS, 1977; Infante and Legator, 1980; PHS, 1979).

TABLE 16 FORECASTED CHANGES IN HUMAN STUDIES

Change	Flag	Time Frame
1. Subchronic Studies--simple, noninvasive neurotoxicology screening tests, applied by paraprofessionals	• Conferences and workshops	1986-91
2. Epidemiology:		
a. Increasing use of the National Death Index as data base increases	• Conferences and workshops	1988-91
b. Decreasing availability of other data on human populations because of privacy concerns by public	1. Privacy Act 2. Legislative changes favoring epidemiology studies	1980-on

Epidemiology is also suffering from public concerns about the invasion of privacy. As a result, valuable historical information that could be accessed through Social Security Numbers is not available for use in these studies.

Eventually epidemiology studies will be facilitated by data in the National Death Index, started in 1979 by the National Center for Health Statistics. At the present time the data base is too small to be of real value.

It is anticipated that subchronic studies will benefit, by the year 2020, from the availability of simple, non-invasive neurotoxicological tests that may be applied by paraprofessionals. These tests will be used for screening people after exposures to detect possible subclinical neurotoxicological effects. It is anticipated that the availability of tests of this sort will generate the need for additional traditional toxicology testing to followup conclusions about unsuspected hazards, based on the screening tests.

Quality Assurance

Major changes in technology related to quality assurance of toxicology testing are not anticipated. Requirements for quality assurance will be provided from two sources. One is compliance with established regulations and Test Standards (EPA, 1979), and the other is the increased scrutiny research is undergoing prior to publication in peer-reviewed journals. A tendency observed by a portion of the toxicology community has been that Governmental pressure on industry to provide support for past or future introduction of chemicals has resulted in the proliferation of published toxicology data which have not undergone the peer review. This has resulted in some cases in the distribution of invalid data. Disagreements and conflicting reports from the toxicology community result, which causes a loss of credibility by toxicology in the public's eyes.

If this situation is recognized by a large enough portion of the scientific and regulatory communities, there may be a tendency in the future to incorporate more peer reviews of data provided by industry to the Government.

Toxicology Data Interpretation

The changes that are anticipated in the area of data interpretation are summarized in Table 17. The interpretation of toxicology data will increasingly utilize computerized, on-line data bases. General toxicology data bases will tend to be more centralized, as demonstrated by the development of the CSIN data base. However, there may be a tendency to develop new data bases dealing with specialty areas within toxicology which are not now covered by the general toxicology data bases.

The use of these data bases will become more common as a result of increasing cost and time for performing toxicology studies. Awareness of data already in the literature will become a major factor in reducing funds expended in toxicology testing.

Structure-activity relationships (SAR) are being converted into on-line data base forms, but are mainly available only for organophosphorus compounds. At present, the use of SAR is limited for other chemicals, but the benefits of

TABLE 17 FORECASTED CHANGES IN INTERPRETATION OF TOXICOLOGY TEST DATA

Change	Flag	Time Frame
1. Structure-Activity Relationships (SAR)		
a. Increased use of SAR in tier approaches	• CIIT SAR Symposium, Feb., 1981	1986-91
b. Increased number of data bases available for SAR use	1. PROPHET and QUASAR on-line systems 2. NCI research data bank	1981-on
2. Data Base Systems:		
a. Centralization of toxicology data bases	• Development of CSIN data base	1980-85
b. Development of specialized data bases to fill gaps in present bases	• Vendor literature	1983-91

using SAR data for prioritizing toxicology testing and applying SAR within tier approaches will motivate the development of SAR data for increasing numbers of other chemical groups.

Factors Influencing Technology Changes

Table 18 summarizes the major factors that influence changes in toxicology testing technology. These consist of knowledge gaps, economic factors, political aspects, industrial pressures and regulatory influences. As discussed above, a major goal of toxicology researchers doing basic research is to fill knowledge gaps. Both basic and applied researchers (including industrial and governmental groups) are pursuing efforts to increase the quality and the quantity of data obtained per test and reduce the time and cost of toxicology testing. Although these efforts will tend to use more resources, the overall result will be the acquisition of more useful information per research dollar.

Public awareness of the significance of potential health and environmental hazards, and fear of unseen threats, result in a significant political input into toxicology testing changes. Recent concerns about the delayed effects (20 years or more) of exposures to hazardous materials will generate the need for additional long-term testing to satisfy the public's concern about exposure to materials having unrecognized health effects. Additional genetic and behavioral toxicology tests will no doubt be added to tests now required for carcinogenicity to prove the safety of new chemicals. In addition, new types of tests may possibly be required in some cases to test for delayed sequelae after even short-term exposures to potentially hazardous materials (i.e., simulating accidental or combat exposures to materials at relatively high concentrations).

A potentially significant political factor might be public concern about exposure to potentially hazardous discharges from toxicology testing facilities. To prevent or minimize these concerns, toxicology facilities may continue to incorporate systems for purification of gaseous and liquid discharges and to eliminate the discharge of hazardous material in solid wastes.

Industry will tend to desire extensive and long-term testing of materials before they are classified as hazardous by regulatory agencies. This is in the hope or expectation of refuting the hazardous properties of chemicals or possibly, just to delay the pending regulatory decision. This pressure will no doubt result in insistence by the regulatory agencies for more testing using the standardized, conventional toxicology tests. This emphasis will tend to minimize acceptance by these agencies of shorter, less costly tests. However, it is likely that industrial and other groups performing applied research will continue to develop and use additional short-term, less costly tests and submit the resulting data as evidence of the safety of materials.

Regulations and guidelines prepared by regulatory agencies will tend to provide standardized test protocols required for compliance. One emphasis will be on the administrative requirements necessary to ensure quality assurance (GLP).

Existing regulations will continue to be implemented and will require additional facilities in the future to provide protection for workers within the facility and the population and environment surrounding it.

TABLE 18 FACTORS INFLUENCING TOXICOLOGY TESTING CHANGES

1. Knowledge Gaps:

   a. Knowledge gaps increase cost and complexity of tests and data interpretation

   b. Basic research will eliminate knowledge gaps (Table 10), reducing cost and increasing accuracy of extrapolation to human health effects.

2. Economics:

   a. Average cost of long-term, two species test is $500,000 to $750,000.

   b. High cost of testing directs technology toward use of:

      - Screening tests
      - Tier approaches
      - Use of SAR
      - More effective utilization of established data bases
      - Better quality control measures to prevent repeating tests

   c. Cost will change protocols to obtain more data per test.

      - More value to data through better statistical treatments
      - More accurate extrapolation to human health effects using new models

3. Political Aspects:

   a. Public concern about exposure to substances that later are classified as potentially hazardous increases needs for:

      - More thorough testing of substances already in environment
      - Tests of genetic, behavioral and other effects (not just carcinogenicity)
      - Tests designed to detect delayed sequelae after short exposures to high concentrations of hazardous substances

   b. Public and governmental concern related to discharge of solid, liquid and gaseous wastes from facilities that test hazardous materials will increase need to incorporate better waste disposal capabilities

4. Industrial Pressure:

   a. Industry desires exhaustive, long-term testing to be completed before substances are declared hazardous.

continued-

Table 18 - continued

b. Regulatory agencies will emphasize those tests that satisfy industrial objections.

c. Industry will strive to develop short-term (less costly) tests to prove substances are not hazardous.

5. Regulatory Influences:

a. Regulatory agencies will formalize protocols and administrative procedures required for good quality assurance.

b. Regulations will maintain importance of well-established, costly tests now used.

Impact of Technology Changes on Resource Requirements

Tables 19 through 22 summarize the effects that the forecasted technology changes, discussed above, may have on future toxicology testing resource requirements. Table 18 summarizes the projected significant changes in requirements for toxicology personnel, while Table 19 lists the impact on requirements for supporting personnel. The effects on requirements for test animals and animal holding facilities are presented in Table 20. Requirements for other supporting facilities are listed in Table 21.

Toxicology Personnel Requirements

Shortages of professionals in the following subdisciplines now exist and are expected to exist well into the 1980's or beyond:

1. Veterinary pathologists
2. Inhalation toxicologists
3. Pharmacokinetists and toxicokinetists
4. Neurotoxicologists
5. Biostatisticians

Technicians and professionals familar with neurophysiological and tissue culture techniques are also in short supply.

An apparently adequate supply of behavioral toxicologists and neuroscientists exists. Neuroscientists may be attracted to neurotoxicology by the availability of research funds. Behavioral toxicologists may play a role in neurotoxicology if they have or acquire training in neuroscience, neuropathology, neurophysiology and neurochemistry.

Requirements for toxicology professionals and technical staff will increase during the next ten years, in part because of increasing numbers of substances that will undergo testing. However, the personnel requirements will increase at a faster rate because of the use of protocols that require more technical judgements on the part of trained professionals. Also, these judgements will be required on a more frequent basis during a given test program than was the case with older protocols. This is due to the greater use of screening tests and tier approaches in test programs that otherwise would not have used so many short-term tests. The use of screening tests and tier approaches adds decision points to the test program after relatively short-term tests. The frequency is increased beyond that previously encountered when decisions were largely restricted to evaluating the results from acute, subacute and chronic tests.

New types of studies and the acquisition of more data during tests also will increase the workload for toxicology personnel. Tests of aged animals, investigations of carcinogenic initiators and promoters (including possible new tests to assess the function of chemicals as initiators and promoters in the presence of other carcinogenic materials), interspecies comparisons and tests of delayed sequelae are all significant new considerations in toxicology testing that affect personnel requirements.

TABLE 19 IMPACT OF TECHNOLOGY CHANGES ON REQUIREMENTS FOR TOXICOLOGY PERSONNEL[a]

Requirements Change	Technology Change	Time Frame
1. Increased demand for toxicology professionals and technicians	a. Increase use of screening tests and tier approaches	1981-on
	b. Increased studies of initiators and promoters	1980-on
	c. Studies of delayed sequelae after short-term exposures	1983-91
	d. Increase in studies of aging effects	1984-86
	e. Validation and use of math models	1981-91
2. Increased demand for pharmacokinetists and toxicokinetists	a. More differential exposure assessments	1980-on
	b. More interspecies comparisons	1980-on
	c. Definition of new carcinogenic detection methods	1983
3. Increased demand for neurotoxicologists	a. Development of new neurotoxicity assay techniques	1980-85
	b. Development of non-invasive screening tests	1988-91
4. Increased demand for trained technicians (paraprofessionals)	a. Use of paraprofessionals to screen tissue samples	1980-on
	b. Development of simple, non-invasive tests for subclinical neurotoxicology screening	1988-2020

(a) Proportional increases in facilities and equipment to support these personnel are assumed.

TABLE 20 IMPACT OF TECHNOLOGY CHANGES ON REQUIREMENTS FOR SUPPORTING PERSONNEL[a]

Requirements Change	Technology Change	Time Frame
1. Increased need for analytical chemists and instrumentation:		
• Contamination Monitoring - Heavy Metals - Organic contaminants	a. GLP requirements	1981-on
• Radionuclide and stable tracer studies	b. More differential exposure route assessments	1981-on
	c. More interspecies comparisons	1981-on
• Environmental monitoring and analysis	d. Increased number of comprehensive relative exposure assessments	1983-90
2. Needs for more broadly trained veterinarians	a. More interspecies comparisons, using new animals species	1981-on
	b. Use of more animals per test	1981-on
3. Increased need for trained quality assurance personnel	a. Increasingly detailed regulations and guidelines	1980-on
	b. Greater use of aged animals	1984-91
4. Additional requirements for computer programmers, math modelers	a. Needs to store more data longer	1981-on
	b. Use of computers for more accurate statistical treatment of data	1981-on
	c. Use of computerized data bases for SAR studies	1981-on
	d. Increasing use of math models to predict toxicology test results	1981-91

(a) Proportional increases in facilities and equipment to support these personnel are assumed.

continued-

Table 20 - continued

Requirements Change	Technology Change	Time Frame
5. Additional requirements for technical information specialists and librarians	a. Greater centralization of data in on-line data bases	1980-on
	b. Possible development of new, specialty data bases	1981-on

TABLE 21 IMPACT OF TECHNOLOGY CHANGES ON REQUIREMENTS FOR ANIMALS AND HOLDING FACILITIES

Requirements Change	Technology Change	Time Frame
1. Greater diversity in: • Species used for testing • Holding facilities	a. More interspecies comparisons	1981-on
	b. Use of species larger than mouse in dosimetry studies	1981-on
	c. Use of hog and minipig for cardiovascular and digestive studies	1981-91
	d. Increased use of smaller primates in behavioral toxicology studies	1981-91
	e. Identification of best species for extrapolation to human effects	1986-91
	f. Use of cellular and other submammalian tests in tier approaches	1980-on
2. Requirements for increased numbers of animals (up to twice the number now used)	a. Use of more control animals per test: • Positive and negative controls • Vehicle, solvent and naive controls	1980-on
	b. Use of larger number of animals exposed to lowest dose	1980-on
	c. Decreased reuse of animals (except primates in some tests)	1980-on
	d. Use of additional screening tests to prioritize substances for testing	1980-on

continued-

Table 21 - continued

Requirements Change	Technology Change	Time Frame
	e. More studies of: • Initiators • Promoters • Aging effects	1980-on
	f. Use of more dose levels per test (4-5 plus controls)	1980-on
	g. Completion of more chronic tests per unit time (length reduce to 1 year)	1980-on
3. Reduced number of animals required for detection of average to low carcinogens	Use of tests using radionuclides to detect carcinogenicity (in place of specific locus test)	1981-91
4. Demand for proportionately more holding facilities	More use of aged animals in tests, resulting in longer animal holding times	1984-86

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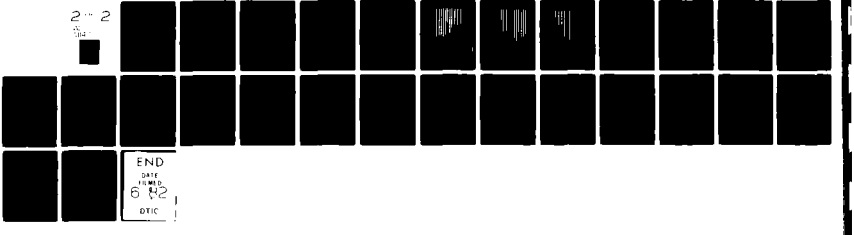

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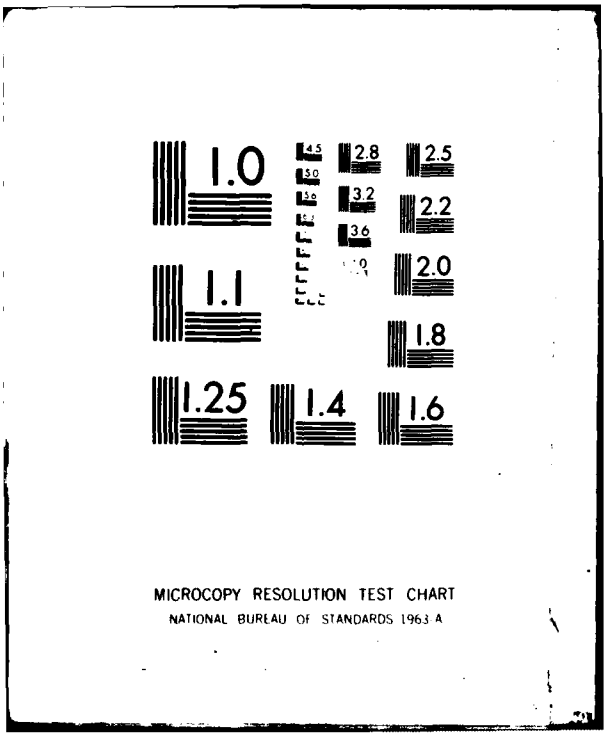
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TABLE 22 IMPACT OF TECHNOLOGY CHANGES ON REQUIREMENTS FOR SUPPORTING FACILITIES

Requirements Change	Technology Change	Time Frame
1. Incorporation of wastewater treatment facilities	1. Discharge regulations 2. Local regulations and restrictions	1982-on
2. Incorporation of improved incineration equipment for disposal of solid wastes	• RCRA	1980-on
3. Incorporation of water purification systems • Animal drinking water • Laboratory supplies	1. Concern about contamination from drinking in long-term tests 2. Tissue assay methods	1981-85
4. Incorporation of more worker protection: • Protective clothing • Ventilation systems (especially in necropsy)	1. Consideration of unknown materials as potentially hazardous 2. Classification of formaldehyde as potential carcinogen	1981-on
5. Increased size and number of computer facilities and related equipment for: • Data storage • Data reduction • Statistical data manipulation • On-line information search	1. Defense against litigation 2. Collection of more data during tests 3. More effective use of existing data base	1981-on
6. Replacement of electron microscopes by light microscopes in histopathology	• Use of new fixatives to improve resolution of light microscopes	1981-84
7. Replacement of free-standing inhalation chambers by modularized inhalation chambers	• Development of new testing facilities using labor-saving designs	1980-on

continued-

Table 22 - continued

Requirements Change	Technology Change	Time Frame
8. Development of core analytical facilities with other analytical support available outside (for GC/MS, etc.)	• Cost-effective response to increased need for analytical data	1981-on
9. Improvement in ventilation, purification of air (especially for behavioral tests) in animal holding/testing areas	• Concern about environmental effects on test results	1986-91
10. Incorporation of tissue storage facilities	• Increased use of biological monitoring for subclinical effects	1981-on
11. Possible incorporation of facilities for training or retraining technicians and professionals in new technologies	1. Development of significant new technologies 2. Personnel requirements not satisfied through universities	1986-91

Supporting Personnel Requirements

Requirements for analytical chemists, quality assurance personnel, computer programmers and math modelers, technical information specialists and librarians, and veterinarians (broadly trained for work with many new species of test animals) will be affected by the forecasted technology changes.

Analytical chemists will be required in increasing numbers to support exposure studies by providing environmental monitoring capabilities. Although some of these measurements will be made outside of the toxicology testing facility, a facility that provides comprehensive toxicology studies will have the analytical personnel and instrumentation required for these studies, either within an in-house "core" analytical group or accessable through an outside source on a cooperative or contractual basis.

Additional analytical requirements will arise from studies involving radionuclides and stable tracers for differential exposure route studies. Also, increased concern about the purity of feed and water will require routine determinations of heavy metals, pesticides, PCB's and estrogens in the food, and chlorinated hydrocarbons in the drinking water. The frequency of these tests will almost certainly make them part of the core analytical group. Analytical determinations of the substances listed above will make heavy use of gas chromatography, high-pressure liquid chromatography and spectroscopy.

Other analytical determinations required on a less frequent basis, and especially those requiring sophisticated instrumentation such as GC/MS and NMR, may be most cost-effectively accomplished using outside analytical services.

Quality assurance personnel increasingly will be needed to ensure that the GLP requirements are satisfied, and that other administrative and technical procedures, specified in test standards and guidelines established by regulatory agencies, are followed.

Computer programmers and math modelers will be required to establish, update and maintain computerized system for data storage, statistical treatment of data, and modeling of toxicology tests. Technical information specialists, possibly using some of the same equipment, will be employed to perform information searches and reference acquisition in support of toxicology professionals. Librarians may provide a valuable service to professional toxicologists by performing searches of key jou[illegible] as they are published, using key words to identify those articles requi[illegible]he toxicologists to maintain their awareness of current events in their [illegible]ch areas.

Broadly trained veterinarians will be required to deal with the new species of animals to be adapted within the next ten years for testing. The diversity in test animals will also have an impact on breeding and holding facilities. This is discussed in greater detail below.

Animal and Animal Holding Facilities Requirements

Increased emphasis on improved statistical treatment of toxicology data will result in the use of up to twice as many animals for some tests as are now used. However, in tests for carcinogenicity, the use of tracers will permit

the use of fewer animals than in the specific locus test now used for the same purpose. In general, more animals will be required to provide: (1) more controls, (2) more lowest dose animals, (3) more dose levels in dose response studies, and (4) more animals for serial sacrifice data.

Other studies will be performed to introduce additional species of test animals. These will include both submammalians (Hydra, bacteria, insects, etc.) and new mammalian species, especially for differential exposure route studies.

The result of these activites will be increases in the space required for animal breeding and holding facilities, and needs for more versatile cages and cage racks.

The space required for holding animals will undergo additional increases when tests of aged animals are performed. For example, tests may start with rats that are 12 to 18 months old, whereas presently rats that are one or two months old are used. Use of aged animals will have a proportionately larger effect on requirements for breeding and holding facilities than would the use of the same number of younger animals.

Requirements for Supporting Facilities

The disposal of waste material generated within toxicology testing facilities will be a significant factor in the allocation of resources. Present incineration systems for disposal of solid wastes (carcasses, bedding material, etc.) cost approximately $350,000, plus energy, operating and maintenance costs. During the next ten years, the cost of disposing of liquid and solid wastes may reach 25% of the overall costs for toxicology testing. This is especially likely if treatment of wastewater (generated in the facility from the washing of animal cages, etc.) must be treated before discharge to municipal sewer systems.

Other significant, but smaller effects, on toxicology resources are the incorporation of equipment for the purification of drinking water and water to be used during various toxicological analyses (tissue studies, etc). Drinking water probably will be treated by ion exchange, carbon adsorption and UV radiation. Water for laboratory tests may be treated by ion exchange and filtration. Within a ten year period, improved ventilation, air purification and noise-control systems may be incorporated in animal breeding and holding areas to eliminate possible effects on test results caused by responses to environmental factors such as odors and noise. Improved ventilation systems will be incorporated in necropsy laboratories for worker portection from formaldehyde vapors.

Other facilities that will grow in importance are the core analytical capabilities and computer facilities for data storage, statistical evaluation of data, online data search and SAR studies. Long-term tissue storage facilities will be required to provide historical reference material.

Some toxicology testing facilities may incorporate some training/retraining capabilities for both professionals and technicians. This is one way of maintaining the effectiveness of already scarce toxicology personnel. Also, these facilities would provide a method by which technicians could be trained

to become paraprofessionals, having sufficient expertise in toxicology to perform routine functions now performed by toxicology professionals. Paraprofessionals could perform screening tests and similar activities to relieve the workload of the more highly-trained professional staff.

Other facility changes that deal with specific aspects of toxicology testing include the transition from free-standing inhalation chambers to modularized chambers and the transition from electron microscopy to light microscopy for many histopathology studies. The latter change will result in significant reductions in equipment and maintenance costs since light microscopes are less expensive to purchase and maintain. Existing toxicology facilities probably will soon make the transition from electron microscopy to light microscopy in this area. Facilities now in the planning stage have the opportunity to begin with the second-generation equipment that improves the resolution of the light microscope.

Conclusions

The approximate period during which the predicted changes in toxicology testing resources will occur are shown graphically in Figure 3. Figure 3 suggests that during the next ten years a number of significant changes in the nature of toxicology testing will have been completed. In actuality, changes will still be occurring at the end of this period. However, changes that can be identified now will have well-defined effects upon resource requirements within the ten year period. There will be a transition to more day-to-day involvement by toxicology professionals in management of test programs. During the test program, they will utilize greater support from professionals and technical staff in the areas of chemistry, veterinary medicine and computer technology. They will be supported by paraprofessionals and technicians who have undergone training in the new testing techniques that have recently been developed, or which will be developed during the next ten years. Toxicology professionals will be better supported by technical information specialists and librarians to help maintain their awareness of current progress in their research areas.

Each of these professionals and supporting personnel will require facilities and equipment in order to perform their function. As a result, by 1991, toxicology testing facilities will be more diverse and have a more interdisciplinary flavor than is now the case.

Requirements for trained toxicology personnel can be satisfied by universities if sufficient funding is available to support undergraduate and graduate studies. However, funding for basic research is scarce, and the cost of toxicology testing, even at the university level is high. Therefore, it may be necessary for universities to conform to GLP and adapt to the confidentiality requirements that are needed in order to compete for testing funds from private industry.

If universities are unable to supply the needed people, the demand for toxicology personnel may force toxicology testing facilities to undertake some form of training or retraining to meet their own needs.

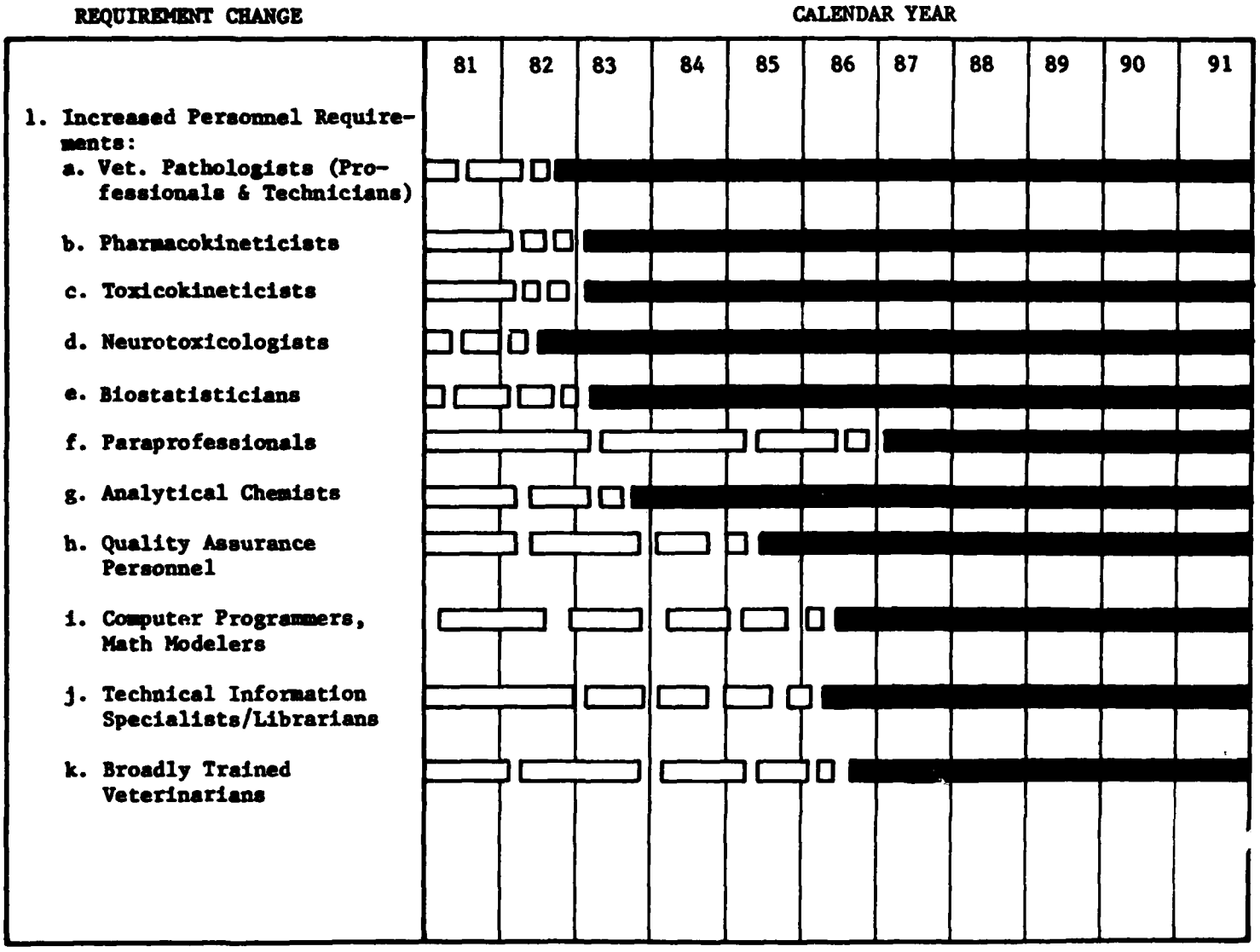

FIGURE 3 IMPACT OF TECHNOLOGY CHANGES ON RESOURCE REQUIREMENTS FOR TOXICOLOGY TESTING

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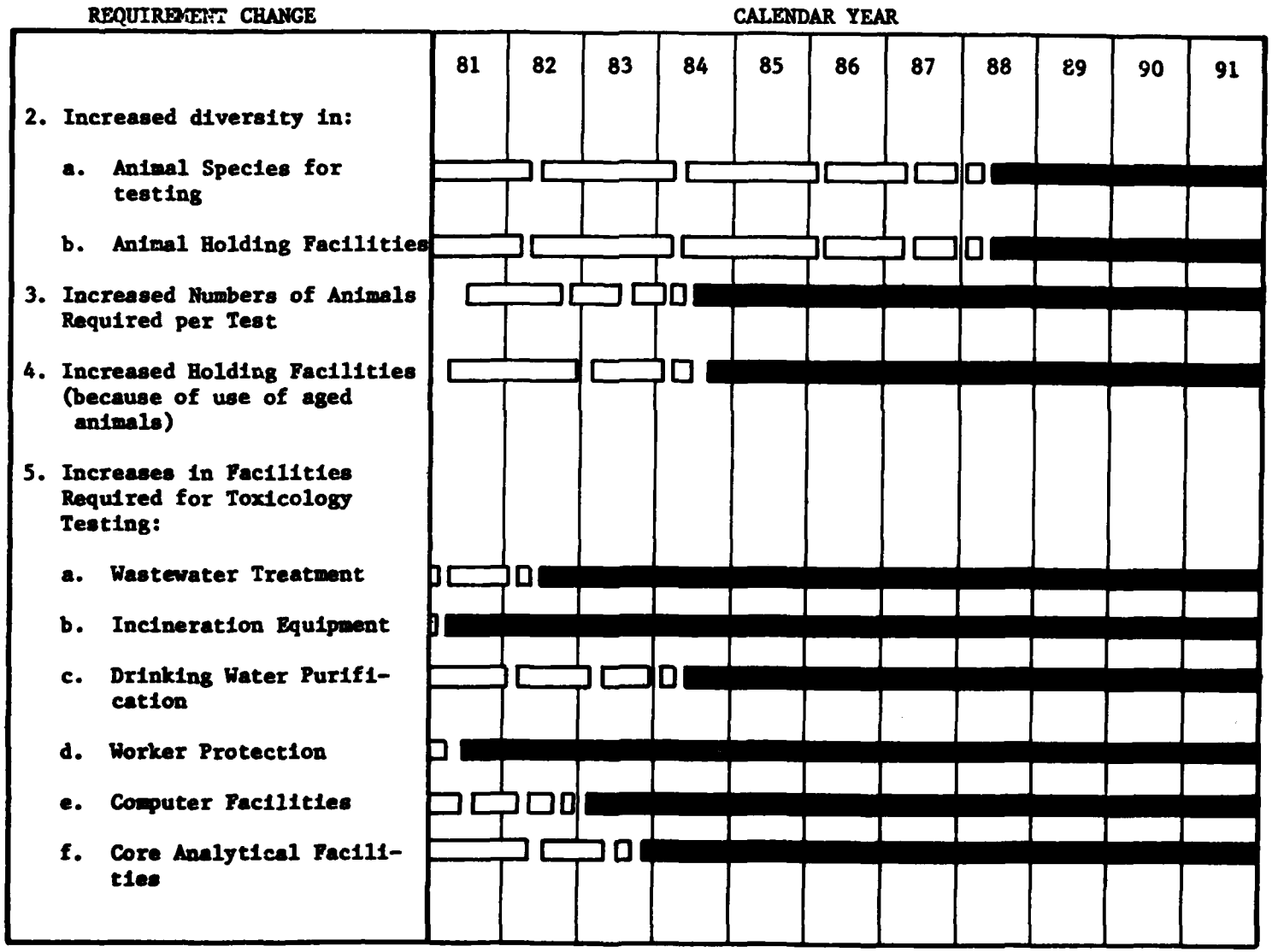

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FIGURE 3 - continued

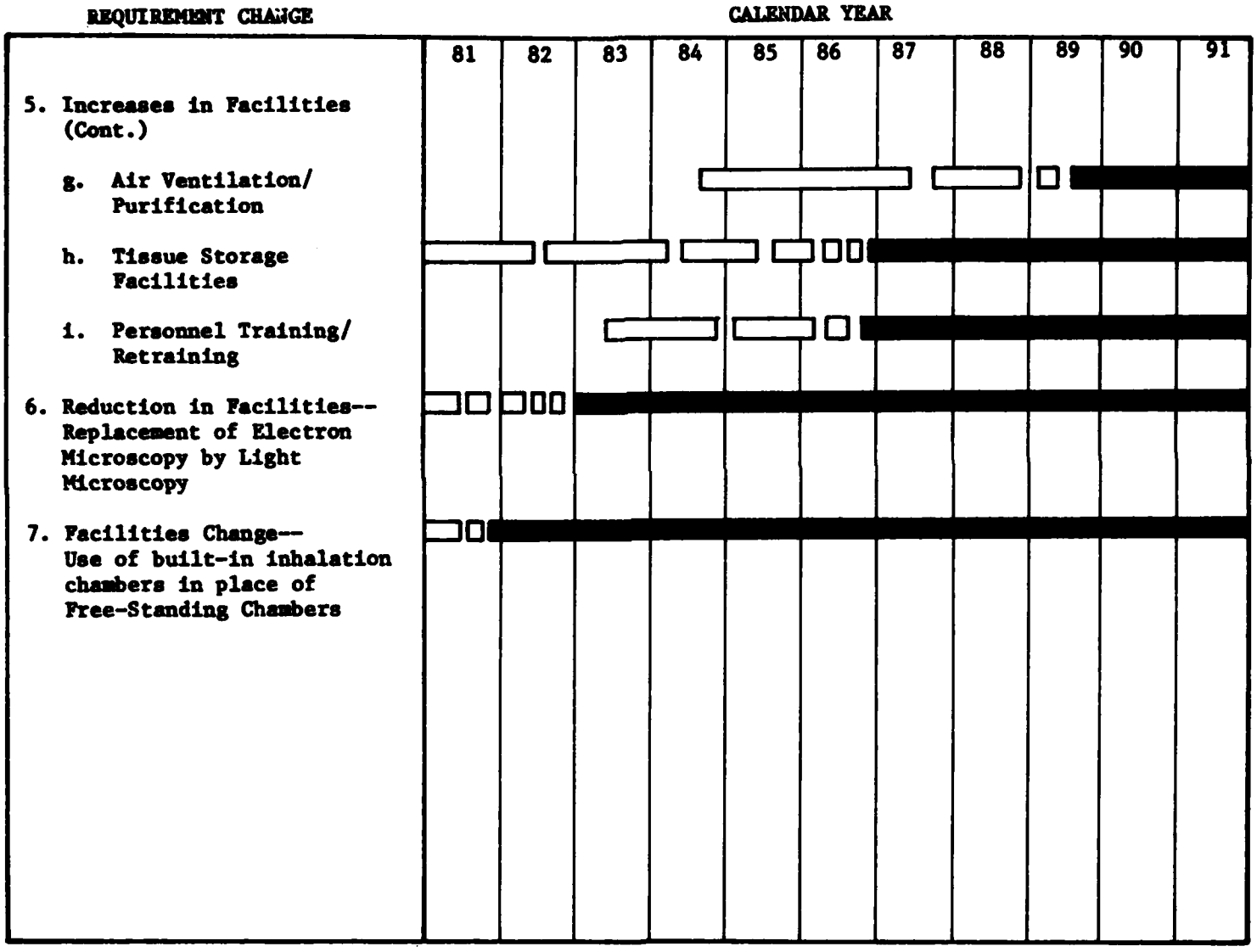

FIGURE 3 - continued

By the end of 1990 it will become increasingly difficult for toxicology testing facilities to provide superior testing capabilities in all areas of toxicology. The costs will have become too great, and the required disciplines too varied. It seems reasonable that toxicology facilities will find it more cost-effective to specialize in certain areas within toxicology. Comprehensive testing programs, requiring the full range of toxicology disciplines and supporting facilities, may be accomplished through cooperative agreements between specialized centers for toxicology testing.

The extremely high cost of waste disposal, as well as costs for other supporting services (computers, analytical facilities, etc.), may be significantly reduced by joint utilization of these services by several toxicology testing facilities. Costs may be significantly reduced by sharing support functions between testing facilities that are located relatively close together. Some supporting functions may be available through other testing or research facilities that do not do toxicology testing, or from outside vendors and services organizations.

This scenario suggests that within the next ten years, toxicology facilities will become increasingly specialized, but will provide, on the whole, a broader range of expertise in toxicology and supporting disciplines than is the case today. These centers may establish cooperative agreements for sharing services. Toxicology testing facilities will probably be served by a group of service organizations in their geographical area who can perform functions such as waste disposal, sophisticated analytical analyses, and so forth, more economically than in-house resources.

Recommendations

The increasing diversity in personnel, instrumentation, facilities, types of tests to be performed, and types of animals to be tested, means that flexibility in all aspects of toxicology testing will be increasingly important. This includes planning, staff organization, physical layout of facilities, and the laboratory equipment. Certain recommendations can be made based on the predicted technology changes and conclusions drawn from them:

1. A plan should be established for determining toxicology resource requirements, including personnel, equipment, expendables and facilities. This plan should be based on specific assumptions that can be used to calculate and update resource requirements, based on technology changes as they occur.

2. Flexibility in the layout of toxicology testing facilities should be emphasized, where possible, to reduce the cost of the changes that will occur during the next ten years. Portability of equipment and facilities should be one of their selection criteria. The arrangements of utilities might be standardized to simplify future rearrangements of toxicology testing areas and other supporting laboratories.

   Modularized offices and laboratories, constructed using movable wall panels, should be considered as methods of providing flexibility to permit changes to be made as responsively and cost-effectively as possible.

Flexibility will be required in animal breeding and holding facilities, since requirements for animals and the facilities to hold them are projected to increase to twice their present levels during the next ten years. These facilities will also have to adapt to the use of more species of animals. These will include larger mammals, smaller primates, aquatic and avian species, and submammalian species (Hydra, insects, bacteria, etc.) for screening tests and tier approaches.

As with offices and laboratories, breeding and holding facilities may benefit through use of modularized designs, movable walls and standardized utilities arrangements.

Cages, cage racks and other equipment should be selected, at least in part, on the basis of their flexibility.

4. Where possible, animal breeding and holding facilities should be located in quiet, well ventilated areas. This will eliminate extraneous effects on animals due to noise and odors. In turn, this will eliminate the need to make future changes when the potential effects of these environmental factors on test results take on a greater criticality (as predicted to happen in six to ten years).

5. Laboratory facilities having designated "clean" and "dirty" areas should be designed with human engineering features to prevent contamination of clean areas through accidents or carelessness on the part of the workers. If these human engineering factors are not included in the design, it should be realized that costs are incurred for establishment of clean/dirty areas, but the objectives for which these areas were incorporated may not be achieved.

In addition to the recommendations listed above, the following considerations for managers and planners of toxicology testing facilities are provided:

1. Flexibility for supporting services may be achieved most readily by providing such support on a centralized basis. For example, gas chromatographic instrumentation may be most effectively utilized during periods of changing needs by locating the instruments in a central location. The opposite case would be distribution of the chromatographs throughout the toxicology facility. It is recognized that some tests will require the use of analytical instrumentation attached to the test chamber to obtain real time data. However, the use, management and upkeep of the instrument generally can be done most effectively when the chromatographs are centrally located.

   This arrangement for management of supporting functions and equipment will minimize equipment purchases in one area, while functionally similar equipment is unused in another area.

2. It is recommended that modular inhalation chambers be considered for new inhalation toxicology facilities, in place of free-standing chambers. This should reduce labor requirements. Advanced fixative methods for histopathology tissue studies with light microscopes, rather than electron microscopes, should be incorporated in new

facilities. The transition to the newer histopathology technology should be included into the plans for existing facilities.

3. Decision-makers and planners should investigate the availability of vendors and service organizations to provide necessary supporting functions to the toxicology testing facilities. These services may include sophisticated analytical analyses, hazardous wastes disposal, training and retraining of personnel, information search and reference acquisition services, searches of specialized journals not covered in the on-line toxicology data bases, and so forth. A continuing effort should be established to monitor the availability of new services, since it is projected that organizations providing these types of services will be created to support major centers of toxicology research.

4. Planners of toxicology facilities should consider the types of toxicology testing to be performed at their facility, and develop strategies that lead to effective capabilities in those technical areas of highest priority. Consideration then should be given to establishing cooperative arrangements with other toxicology testing facilities to perform testing that would be required on a less frequent basis, or that has a lower priority. Recognition of the high cost and scarcity of resources required in toxicology means that planners should emphasize specialization rather than attempting to establish a comprehensive toxicology capability that might result in mediocre capabilities in all areas.

5. Planners of toxicology facilities should also maintain an awareness of local restrictions on the disposal of solid and liquid wastes. A comparative analysis of disposal strategies, including the use of in-house facilities, contractual service organizations, and cooperative agreements with other toxicology facilities having waste disposal equipment, should be performed. Planners should be alert to possible changes in local regulations that will significantly restrict waste disposal, increase its cost, or in other ways impede the performance of the facility. These upcoming changes, if they can be identified, could significantly affect the outcome of the comparative analysis.

REFERENCES

This reference section includes all references and specific sources of information cited in the regulatory changes and technology changes sections of the report respectively. An alphabetical listing of these and "suggested further reading" is provided in the Bibliography.

Regulatory Changes

Anon. 1980d. HHS puts out a "wish list" of 1990 objectives for control of toxics. Pesticide and Toxic Chemical News. December 10. pp. 21-22.

Anon. 1979. The chemicals industry and the environment. Industry and Environment. Oct/Nov/Dec. 2:4.

Barnes D. 1981. Science Advisor, Office of the Assistant Administrator for Toxic Substances, U.S. EPA. Futures research, personal communication to A. Cywin. January 13.

Blumenthal H. 1981. Director, Division of Toxicology, U.S. Food and Drug Administration. Futures research, personal communication to A. Cywin. January 14.

Cannon L. 1981. Reagan wants quick start on cost-cutting. Washington Post. January 16.

Chemical Manufacturers Association (CMA). 1980a. Comments of the Chemical Manufacturers, Inc., on IRLG scientific issues for primary skin irritation, subchronic ingestion, subchronic dermal, and two-generation reproduction studies. Washington, DC. January 28.

Chemical Manufacturers Association (CMA). 1980b. Comments of the Chemical Manufacturers Association on EPA's advance notice of proposed rulemaking concerning the commercial and asbestos use of asbestos fibers. Washington, DC. February 19.

Chemical Manufacturers Association (CMA). 1980c. Comments of the Chemical Manufacturers Association, Inc., on EPA proposed test rule and exemptions procedures under Section 4 of the TSCA. Washington, DC. October 31.

Chemical Manufacturers Association (CMA). 1979. Comments of the Chemical Manufacturers Association on draft IRLG guidelines for selected acute toxicity tests. Washington, DC. December 3.

Chu K. 1981. Director, Health Effects Division, Occupational Safety and Health Administration, U.S. Department of Labor. Futures research, personal communication to A. Cywin. January 13.

Conservation Foundation. 1978. Approaches for developing testing guidelines under the Toxic Substances Control Act with 21 public comments (Draft Report). Washington, DC. June.

Council on Environmental Quality (CEQ). 1975. Carcinogens in the environment. Reprinted from Sixth Annual Report of the Council on Environmental Quality. Washington, DC: U.S. Government Printing Office, Stock No. 041-011-00030-1.

Cywin A. 1981. Personal communication to Life Systems, Inc. Draft input to impact of changes Final Report. Contract DAMD17-81-C-1013. January.

Cywin A. 1980. Clean water - past, present, future. Federal Water Quality Association Newsletter. 8:3 pp. 2-4. December.

Doull J, Malone, AK. 1980. Summary of the task group. In: Long-Range Environmental Outlook. Washington, DC: National Academy of Sciences. pp. 136-143.

Environmental Protection Agency. 1980a. Operating year guidance for fiscal year 1981. Washington, DC: U.S. EPA.

Environmental Protection Agency. 1980b. Research Outlooks 1980. Washington, DC: Office of Research and Development, U.S. EPA 600/9-80-006.

Environmental Protection Agency. 1979a. Proposed health effects standards for toxic substances control act test rules and proposed good laboratory practice standards for health effects. Federal Register, July 26, 1978, 44:44054-44093.

Environmental Protection Agency. 1979b. National interim primary drinking water regulations; control of trihalomethanes in drinking water; Final Rule. Federal Register. 44:231. pp. 68690-68707. November 29.

Environmental Protection Agency. 1979c. A handbook of key Federal Regulations and criteria for multimedia environmental controls. Industrial Environmental Research Laboratory, RTP, NC, EPA-600/7-79-175.

Gibson JE. 1980. Toxic substances: Future trends in the development and use of potentially toxic substances. In: Long-Range Environmental Outlook. Washington, DC: National Academy of Science. pp 118-131.

Greve F. 1981. How can Reagan alter the EPA? Akron Beacon Journal (Knight-Ridder Newspapers), Akron, OH. January 18. pp. C1 and C4.

Hill R. 1981. Science Advisor, Office of the Assistant Administrator for Pesticides and Toxic Substances, U.S. EPA. Futures research personal communication to A. Cywin. January 12.

Hilts PJ. 1981. Agencies rush rules to beat inaugural gun. The Washington Post. January 18. pp. A14.

Interagency Regulatory Liaison Group (IRLG). 1979. Scientific bases for identification of potential carcinogens and estimation of risks. Report of the Interagency Regulatory Liaison Group, Work Group on Risk Assessment. J. Natl. Cancer Inst. 63(1):240.

Laubach G. 1980. State-minded scientific orthodoxy. Excerpts of presentation made at a meeting of the Industrial Research Institute. Chemical & Engineering News. pp. 5. November 10.

Lee C. 1981. Senior Science Advisor, Health and Environmental Review Division, Office of Toxic Substances, U.S. EPA. Futures research, personal communication to J. Glennon. January 28.

McKinnon H. 1981. Office of Research and Development, U.S. EPA. Futures research, personal communication to A. Cywin. January 12.

Occupational Safety and Health Administration (OSHA). 1980. Identification, classification and regulation of potential occupational carcinogens. Federal Register, January 22, 1980, 29CFR1990.

Organization for Economic Cooperation and Development (OECD). 1980. OECD high level meeting on chemicals, 19th/21st May, 1980. Press Release. Paris. May 21.

Organization for Economic Cooperation and Development (OECD). 1979. OECD short term and long term toxicology groups (Final Report). December 31.

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peto J, Richards S, Wahrendorf J. 1980. Annex: Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals in Humans, Supplement 2, Long-term and short-term screening assays for carcinogens; a critical appraisal. Lyon, International Agency for Research on Cancer.

Sinclair W. 1981. Chemical industry to have powerful voice about new EPA Chief. Washington Post. January 15. pp. A8.

Smalley V. 1981. United States Regulatory Council. Futures research, personal communication to A. Cywin. January 13.

Spaulding J. 1981. Director, Research, Evaluation and Inspection under Deputy Administrator for Science, Food Sciences and Quality Service, U.S. Department of Agriculture. Futures research, personal communication to A. Cywin. January 14.

Supreme Court of the United States. 1980. Argued October 10, 1979, decided July 2, 1980. Syllabus. Industrial Union Department, AFL-CIO v. American Petroleum Institute et al. pp. 21-22. No. 78-911.

Ulvedahl F. 1981. Office of Research and Development, U.S. EPA. Futures research, personal communication to J. Glennon. January 15.

United States Regulatory Council. 1979. Statement on Regulations of Chemical Carcinogens; Policy and Request for Public Comments. Federal Register, October 17, 1979, 44:60038-60049.

Technology Changes

Aaron CS, Lee WR. 1978. Molecular dosimetry of the mutagen ethyl methanesulfonate in Drosophila melanogaster spermatozoa: Linear relation of DNA alkylation per sperm cell (dose) to sex-linked recessive lethals. Mutation Res. 49:27-44.

Arcos J, Argus M, Wolf G. 1968. Chemical induction of cancer: Structural bases for biological mechanisms. Vol. 1. New York: Academic Press, pp. 440.

Arrhenius E. 1974. Comparative metabolism of aromatic amines. In: Chemical Carcinogenesis Essays. Lyon, France: International Agency for Research on Cancer, WHO. pp. 3.

Association of Food and Drug Officials of the United States. 1959. Appraisal of the safety of chemicals in food, drugs and cosmetics. Topeka, KS.

Bar-Shalom Y, Budenaers D, Schainker R, Segall A. 1975. Handbook of statistical tests for evaluating employee exposure to air contaminants. Cincinnati, OH: U.S. DHEW, NIOSH. Pub. No. 75-147.

Berky and Sherrod, eds. 1977. Short-term in vitro testing for carcinogenesis, mutagenesis and toxicity. Philadelphia, PA: The Franklin Institute Press.

Calabrese EJ. 1978. Methodological approaches to deriving environmental and occupational health standard. New York: John Wiley & Sons.

Ekel G, Teichner W. 1976. An analysis and critique of behavioral toxicology in the U.S.S.R. Cincinnati, OH: DHEW (NIOSH). Publication No. 77-160.

Environmental Protection Agency. 1979a. Proposed health effects standards for toxic substances control act test rules and proposed good laboratory practice standards for health effects. July 26, 1979. Federal Register 44:44054-44093.

Fiserova-Bergerova V. 1976. Mathematical modeling of inhalation exposure. Jour. of Combustion Toxicology. 3:201-210.

Food Safety Council. 1980. Proposed system for food safety assessment. Final Report of the Scientific Committee of the Food Safety Council. Washington, DC. June.

Goldberg, ed. 1974. Carcinogenesis testing of chemicals. Cleveland, OH: CRC Press.

Hodgson, Bend, Philpot, eds. 1980. Review in biochemical toxicology. Elsevier/ North Holland, New York, NY.

Infante PF, Legator MS, eds. 1980. Proceedings of a workshop on methodology for assessing reproductive hazards in the workplace. Cincinnati, OH: DHHS (NIOSH). Pub. no. 81-100.

Interagency Regulatory Liaison Group (IRLG). 1979. Scientific bases for identification of potential carcinogens and estimation of risks. Report of the Interagency Regulatory Liaison Group, Work Group on Risk Assessment, Washington, DC. February 17.

Kraybill and Mehlman, eds. 1977. Advances in modern toxicology, Vol. 3, Environmental Cancer. John Wiley & Sons, New York, NY.

Lee SD, ed. 1977. Biochemical effects of environmental pollutants. Ann Arbor Science Publishers, Inc., Ann Arbor, MI.

Lee WR. 1978. Dosimetry of chemical mutagens in eukaryote germ cells. In: Chemical Mutagens, Vol. 5. A. Hollaender and FJ. deSerres, eds. Plenum Publishing Corp. pp. 177-202.

Malins and Jensen, eds. 1981. Aquatic toxicology. Elsevier/North Holland, New York, NY. (First issue of this new journal scheduled for publication in February, 1981).

National Academy of Sciences. 1977a. Principles and procedures for evaluating the toxicity of household substances. Washington, DC: National Academy of Sciences.

National Academic Sciences. 1977b. The future of animals, cells, models, and systems in research, development, education and testing. Washington, DC: National Academy of Sciences pp. 152-169.

National Academy of Sciences. 1975. Principles for evaluating chemicals in the environment. Washington, DC: National Academy of Sciences.

National Academy of Sciences. (Undated). Animal Models for Biomedical Research, I, II, III, IV. Washington, DC: National Academy of Sciences.

Public Health Service, U.S. DHEW. 1979. National toxicology program, fiscal year 1980 annual plan. Washington, DC: U.S. Government Printing Office. Publication NTP-79-7.

Ramsey JC, Park CN, Ott M, Gehring PJ. 1979. Carcinogenic risk assessment: Ethylene dibromide. Toxicol. Appl. Pharmacol. 47:411-414.

Reeves AL, ed. 1981. Toxicology: Principles and practice, Vol. 1. John Wiley & Sons, New York, NY.

Spencer PS, Schaumburg HH. 1980. Experimental and clinical neurotoxicology. Baltimore, MD: Williams and Wilkins Co. (Chapters 7, 48-56, 60).

Staffa and Mehlman, eds. 1979. Innovations in cancer risk assessment (ED_{01} study). Park Forest South, IL: Pathotox Publishers, Inc.

Van Ryzin J. 1980. Quantitative risk assessment. J. Occupational Med. 22:321-326.

BIBLIOGRAPHY

This bibliography provides alphabetical listing of references and other information sources relevant to this report. It includes: all references cited in the report; references reviewed for this task but not cited; and references identified by contributors to this report as "suggested further reading." The bibliography is divided into two sections; regulatory changes and technology changes. Where references are relevant to both topics they are included on both lists.

Regulatory Changes

Anon. 1980a. Regulatory Agencies told to be flexible. Chemical & Engineering News. June 23. pp. 11.

Anon. 1980b. Fundamental Regulatory Issues under Consideration by Panel of Congress' OTA. Pesticide & Toxic Chemical News. Washington, DC. December 10. pp. 3-5.

Anon. 1980c. Results aren't in yet on Ames Tests. Gene-Tox Conference is told. Pesticide and Toxic Chemical News. Washington, DC. December 10 pp. 5-8.

Anon. 1980d. HHS puts out a "wish list" of 1990 objectives for control of toxics. Pesticide and Toxic Chemical News. December 10. pp. 21-22.

Anon. 1979. The chemicals industry and the environment. Industry and Environment. Oct/Nov/Dec. 2:4.

Barnes D. 1981. Science Advisor, Office of the Assistant Administrator for Toxic Substances, U.S. EPA. Futures research, personal communication to A. Cywin. January 13.

Blumenthal H. 1981. Director, Division of Toxicology, U.S. Food and Drug Administration. Futures research, personal communication to A. Cywin. January 14.

Cannon L. 1981. Reagan wants quick start on cost-cutting. Washington Post. January 16.

Cetron MJ, Sugarek SE. 1980. A forecast of future environmental protection requirements and their possible implications for Army research. Vol. I. Arlington, VA: Forecasting International, Ltd. U.S. Army Contract No. DACA 88-79-C-0008. February 14.

Chemical Manufacturers Association (CMA). 1980a. Comments of the Chemical Manufacturers, Inc., on IRLG scientific issues for primary skin irritation, subchronic ingestion, subchronic dermal, and two-generation reproduction studies. Washington, DC. January 28.

Chemical Manufacturers Association (CMA). 1980b. Comments of the Chemical Manufacturers Association on EPA's advance notice of proposed rulemaking concerning the commercial and asbestos use of asbestos fibers. Washington, DC. February 19.

Chemical Manufacturers Association (CMA). 1980c. Comments of the Chemical Manufacturers Association, Inc., on EPA proposed test rule and exemptions procedures under Section 4 of the TSCA. Washington, DC. October 31.

Chemical Manufacturers Association (CMA). 1979. Comments of the Chemical Manufacturers Association on draft IRLG guidelines for selected acute toxicity tests. Washington, DC. December 3.

Chu K. 1981. Director, Health Effects Division, Occupational Safety and Health Administration, U.S. Department of Labor. Futures research, personal communication to A. Cywin. January 13.

Conservation Foundation. 1978. Approaches for developing testing guidelines under the Toxic Substances Control Act with 21 public comments (Draft Report). Washington, DC. June.

Council on Environmental Quality (CEQ). 1975. Carcinogens in the environment. Reprinted from Sixth Annual Report of the Council on Environmental Quality. Washington, DC: U.S. Government Printing Office, Stock No. 041-011-00030-1.

Cywin A. 1981. Personal communication to Life Systems, Inc. Draft input to impact of changes Final Report. Contract DAMD17-81-C-1013. January.

Cywin A. 1980. Clean water - past, present, future. Federal Water Quality Association Newsletter. 8:3 pp. 2-4. December.

Deland MR. 1980. The Clean Air Act - major amendments likely. Regulatory Alert.

Doull J, Malone, AK. 1980. Summary of the task group. In: Long-Range Environmental Outlook. Washington, DC: National Academy of Sciences. pp. 136-143.

Environmental Protection Agency. 1980a. Operating year guidance for fiscal year 1981. Washington, DC: U.S. EPA.

Environmental Protection Agency. 1980b. Research Outlooks 1980. Washington, DC: Office of Research and Development, U.S. EPA 600/9-80-006.

Environmental Protection Agency. 1980c. Mutagenicity risk assessments; proposed guidelines. Federal Register, November 13, 1980. 45:221:74984-74988.

Environmental Protection Agency. 1980d. Seventh Report of the Interagency Testing Committee to the Administrator; Receipt of report and request for comments regarding priority list chemicals. Federal Register, November 25, 1980, 45:78432-78446.

Environmental Protection Agency. 1979a. Proposed health effects standards for toxic substances control act test rules and proposed good laboratory practice standards for health effects. Federal Register, July 26, 1978, 44:44054-44093.

Environmental Protection Agency. 1979b. National interim primary drinking water regulations; control of trihalomethanes in drinking water; Final Rule. Federal Register. 44:231. pp. 68690-68707. November 29.

Environmental Protection Agency. 1979c. A handbook of key Federal Regulations and criteria for multimedia environmental controls. Industrial Environmental Research Laboratory, RTP, NC, EPA-600/7-79-175.

Environmental Protection Agency. 1978. Pesticide programs: Proposed guidelines for registering pesticides in the U.S.; Hazard evaluation: Humans and domestic animals. Federal Register, August 22, 1978. 43:37336-37403.

Food Safety Council. 1980. Proposed system for food safety assessment. Final Report of the Scientific Committee of the Food Safety Council. Washington, DC. June.

Gibson JE. 1980. Toxic substances: Future trends in the development and use of potentially toxic substances. In: Long-Range Environmental Outlook. Washington, DC: National Academy of Science. pp 118-131.

Greve F. 1981. How can Reagan alter the EPA? Akron Beacon Journal (Knight-Ridder Newspapers), Akron, OH. January 18. pp. C1 and C4.

Gusman S. 1980. Discussant's remarks on the paper by J. B. Gibson. In: Long-Range Environmental Outlook. National Academy of Sciences. Washington, DC. pp. 132-135.

Hill R. 1981. Science Advisor, Office of the Assistant Administrator for Pesticides and Toxic Substances, U.S. EPA. Futures research personal communication to A. Cywin. January 12.

Hilts PJ. 1981a. Agencies rush rules to beat inaugural gun. The Washington Post. January 18. pp. A14.

Hilts PJ. 1981b. Animal tests are found good indicator of hazards. The Washington Post. January 20. pp. A2.

Interagency Regulatory Liaison Group (IRLG). 1979. Scientific bases for identification of potential carcinogens and estimation of risks. Report of the Interagency Regulatory Liaison Group, Work Group on Risk Assessment. J. Natl. Cancer Inst. 63(1):240.

Laubach G. 1980. State-minded scientific orthodoxy. Excerpts of presentation made at a meeting of the Industrial Research Institute. Chemical & Engineering News. pp. 5. November 10.

Lee C. 1981. Senior Science Advisor, Health and Environmental Review Division, Office of Toxic Substances, U.S. EPA. Futures research, personal communication to J. Glennon. January 28.

McKinnon H. 1981. Office of Research and Development, U.S. EPA. Futures research, personal communication to A. Cywin. January 12.

National Academy of Sciences. 1975. Decision making for regulating chemicals in the environment. Washington, DC: National Academy of Sciences.

Occupational Safety and Health Administration (OSHA). 1980. Identification, classification and regulation of potential occupational carcinogens. Federal Register, January 22, 1980, 29CFR1990.

Omang J. 1981. Heartened EPA puts bloom back on rose as it adds up gains. The Washington Post. January 20. pp. A2.

Organization for Economic Cooperation and Development (OECD). 1980. OECD high level meeting on chemicals, 19th/21st May, 1980. Press Release. Paris. May 21.

Organization for Economic Cooperation and Development (OECD). 1979. OECD short term and long term toxicology groups (Final Report). December 31.

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peto J, Richards S, Wahrendorf J. 1980. Annex: Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals in Humans, Supplement 2, Long-term and short-term screening assays for carcinogens; a critical appraisal. Lyon, International Agency for Research on Cancer.

Public Law 96-502. 1980. The Safe Drinking Water Act, as amended December 5, 1980, 94 Stat. 2739.

Public Law 95-109. 1977. The Clean Air Act, as amended August, 1977, 91 Stat. 1393.

Public Law 95-217. 1977. The Clean Water Act, as amended December, 1977. 91 Stat. 1566.

Public Law 94-469. 1976. The Toxic Substances Control Act, as amended, October, 1976. 90, Stat. 2003.

Public Law 94-580. 1976. The Solid Waste Act (Resources Conservation and Recovery Act), as amended, October, 1976, 90 Stat. 2795.

Public Law 94-140. 1975. The Federal Environmental Pesticide Control Act (Federal Insecticide, Fungicide and Rodenticide Act), as amended, November, 1975, 89 Stat. 751.

Public Law 91-596. 1970. The Occupational Safety and Health Act, as amended, December, 1970, 84 Stat. 1590.

Sinclair W. 1981. Chemical industry to have powerful voice about new EPA Chief. Washington Post. January 15. pp. A8.

Smalley V. 1981. United States Regulatory Council. Futures research, personal communication to A. Cywin. January 13.

Spaulding J. 1981. Director, Research, Evaluation and Inspection under Deputy Administrator for Science, Food Sciences and Quality Service, U.S. Department of Agriculture. Futures research, personal communication to A. Cywin. January 14.

Supreme Court of the United States. 1980. Argued October 10, 1979, decided July 2, 1980. Syllabus. Industrial Union Department, AFL-CIO v. American Petroleum Institute et al. pp. 21-22. No. 78-911.

Ulvedahl F. 1981. Office of Research and Development, U.S. EPA. Futures research, personal communication to J. Glennon. January 15.

United States Regulatory Council. 1980a. An inventory of innovative techniques, 1978-1980. Washington, DC.

United States Regulatory Council. 1980b. Regulatory reform highlights. An inventory of initiatives, 1978-1980. Washington, DC.

United States Regulatory Council. 1980c. Report from the director. Washington, DC. July.

United States Regulatory Council. 1980d. Regulating with common sense: a progress report on innovative regulatory techniques. Washington, DC.

United States Regulatory Council. 1980e. Calendar of Federal Regulations. Federal Register, November 25, 1980, 45:77701-78115.

United States Regulatory Council. 1979. Statement on Regulations of Chemical Carcinogens; Policy and Request for Public Comments. Federal Register, October 17, 1979, 44:60038-60049.

Technology Changes

Aaron CS, Lee WR. 1978. Molecular dosimetry of the mutagen ethyl methanesulfonate in Drosophila melanogaster spermatozoa: Linear relation of DNA alkylation per sperm cell (dose) to sex-linked recessive lethals. Mutation Res. 49:27-44.

Arcos J, Argus M, Wolf G. 1968. Chemical induction of cancer: Structural bases for biological mechanisms. Vol. 1. New York: Academic Press, pp. 440.

Arrhenius E. 1974. Comparative metabolism of aromatic amines. In: Chemical Carcinogenesis Essays. Lyon, France: International Agency for Research on Cancer, WHO. pp. 3.

Association of Food and Drug Officials of the United States. 1959. Appraisal of the safety of chemicals in food, drugs and cosmetics. Topeka, KS.

Bar-Shalom Y, Budenaers D, Schainker R, Segall A. 1975. Handbook of statistical tests for evaluating employee exposure to air contaminants. Cincinnati, OH: U.S. DHEW, NIOSH. Pub. No. 75-147.

Baselt RC. 1980. Biological monitoring methods for industrial chemicals. Davis CA: Biomedical Publications.

Beethe RL, Wolff RK, Griffis LC, Hobbs CH, McClennan RO. 1979. Evaluation of a recently designed multi-tiered exposure chamber. Albuquerque, NM: Inhalation Tox. Res. Inst., Lovelace Biomedl. Env. Res. Inst. Report LF-67, UC-48.

Berky and Sherrod, eds. 1977. Short-term in vitro testing for carcinogenesis, mutagenesis and toxicity. Philadelphia, PA: The Franklin Institute Press.

Berlin A, Wolff A, Husegawa Y. 1979. The use of biological specimens for the assessment of human exposure to environmental pollutants. Boston, MA: The Hague Press.

Brusick D. 1980. Principles of genetic toxicology. New York: Plenum Press.

Calabrese EJ. 1978. Methodological approaches to deriving environmental and occupational health standard. New York: John Wiley & Sons.

Conney AH, Levin W. 1974. Carcinogen metabolism in experimental animals and man. In: Chemical Carcinogenesis Essays. Lyon, France: International Agency for Research on Cancer, WHO. p. 3.

Conservation Foundation. 1978. Approaches for developing testing guidelines under the Toxic Substances Control Act with 21 public comments (Draft Report). Washington, DC. June.

Department of Health, Education and Welfare, NIOSH. 1978. Occupational health in health service areas: Handbook for planning. Cincinnati, OH: DHEW (NIOSH) Publication No. 78-203.

Department of Health Education and Welfare, NCI. 1976. NCI guidelines for carcinogen bioassay in small rodents. DHEW (NIH) Publication No. 76-801.

Department of Health, Eduction and Welfare. 1964. Smoking and health. Report of the Advisory Committee to the Surgeion General of the Public Health Service. USPHS Pub. No. 1103, U.S. Government Printing Office, Washington, DC.

Doull J, Malone AK. 1980. Summary of the task group. In: Long-Range Environmental Outlook. Washington, DC: National Academy of Sciences. pp. 136-143.

Ekel G, Teichner W. 1976. An analysis and critique of behavioral toxicology in the U.S.S.R. Cincinnati, OH: DHEW (NIOSH). Publication No. 77-160.

Environmental Protection Agency. 1981. Current status of bioassays in genetic toxicology. Proceedings of a conference at the National Academy of Sciences, December 3-5, 1980. (In Press).

Environmental Protection Agency. 1980. Mutagenicity risk assessments; proposed guidelines. November 13, 1980. Federal Register. 45:74984-74988.

Environmental Protection Agency. 1979a. Proposed health effects standards for toxic substances control act test rules and proposed good laboratory practice standards for health effects. July 26, 1979. Federal Register 44:44054-44093.

Environmental Protection Agency. 1978. Pesticide programs: Proposed guidelines for registering pesticides in the U.S., Hazard evaluation: Humans and domestic animals. August 22, 1978. Federal Register, 43:37336-37403.

Fiserova-Bergerova V. 1976. Mathematical modeling of inhalation exposure. Jour. of Combustion Toxicology. 3:201-210.

Food and Drug Administration. 1979. Outline of toxicological testing, 1977, as cited by Committee on Agriculture, Nutrition and Forestry. U.S. Senate. pp. 64-65. (Unpublished)

Food and Drug Administration. 1977. Outline of toxicological testing. (Unpublished)

Food & Drug Administration. Undated. Guidelines for preclinical toxicity testing of investigational drugs for human use. (Unpublished)

Food Safety Council. 1980. Proposed system for food safety assessment. Final Report of the Scientific Committee of the Food Safety Council. Washington, DC. June.

Goldberg, ed. 1974. Carcinogenesis testing of chemicals. Cleveland, OH: CRC Press.

Greenhouse DD. 1980. Trends in primate imports into the United States, 1979. ILAR News. 03:2-3:27.

Gusman S. 1980. Discussant's remarks on the paper by J. B. Gibson. In: Long-Range Environmental Outlook. National Academy of Sciences. Washington, DC. pp. 132-135.

Hodge HC. 1960. Proceedings of a symposium on problems in toxicology. Federation Proceedings, Supplement No. 4, 19:50.

Hodgson, Bend, Philpot, eds. 1980. Review in biochemical toxicology. Elsevier/ North Holland, New York, NY.

Hushon JM, Clerman JR, Wagner, BO. 1979. Tiered testing for chemical hazard assessment. Environ. Sci. and Technol. 13:10:1202-1207.

Infante PF, Legator MS, eds. 1980. Proceedings of a workshop on methodology for assessing reproductive hazards in the workplace. Cincinnati, OH: DHHS (NIOSH). Pub. no. 81-100.

Interagency Regulatory Liaison Group (IRLG). 1979. Scientific bases for identification of potential carcinogens and estimation of risks. Report of the Interagency Regulatory Liaison Group, Work Group on Risk Assessment, Washington, DC. February 17.

Kraybill and Mehlman, eds. 1977. Advances in modern toxicology, Vol. 3, Environmental Cancer. John Wiley & Sons, New York, NY.

Lee SD, ed. 1977. Biochemical effects of environmental pollutants. Ann Arbor Science Publishers, Inc., Ann Arbor, MI.

Lee WR. 1978. Dosimetry of chemical mutagens in eukaryote germ cells. In: Chemical Mutagens, Vol. 5. Ed. by A. Hollaender, ed. Plenum Publishing Corp. pp. 177-202.

Lee WR. 1976. Chemical mutagenesis. In: M. Ashburner and E. Novitski (eds.) The Genetics and Biology of Drosophila. Academic Press, NY. pp. 1299-1341.

Lee WR. 1976 Molecular dosimetry of chemical mutagens: Determination of molecular dose to the germ line. Mutation Res. 38:311-316.

Lee WR. 1975. Comparison of the mutagenic effects of chemicals and ionizing radiation using Drosophila melanogaster test systems. Radiation Research, Biomedical, Chemical and Physical Perspectives. Academic Press, NY. pp. 976-983.

Linch AL, ed. 1974. Biological monitoring for industrial chemical exposure control. CRC Press, Cleveland, OH.

Maclure KM, MacMahon, B. 1980. An epidemiologic perspective of environmental carcinogenesis. Epidemiology Review. 2:19-48.

MacMahon B. 1979. Strengths and limitations of epidemiology. In: The National Research Council in 1979. The National Academy of Sciences. Washington, DC. pp. 91.

Malins and Jensen, eds. 1981. Aquatic toxicology. Elsevier/North Holland, New York, NY. (First issue of this new journal scheduled for publication in February, 1981).

Montesano R, Magee PN. 1974. Comparative metabolism in vitro of nitrosamines in various animal species including man. In: Chemical Carcinogenesis Essays. Lyon, France: International Agency for Research on Cancer, WHO. pp. 3.

Murrill EA, Woodhours EJ, Olin SS, Jameson CW. 1980. Carcinogenesis testing and analytical chemistry. Anal. Chem. 52:1188A.

National Academy of Sciences. 1980. Laboratory animal management: Nonhuman primates. In: ILAR News. 23(2-3):P2-P44.

National Academy of Sciences. 1977a. Principles and procedures for evaluating the toxicity of household substances. Washington, DC: National Academy of Sciences.

National Academic Sciences. 1977b. The future of animals, cells, models, and systems in research, development, education and testing. Washington, DC: National Academy of Sciences pp. 152-169.

National Academy of Sciences. 1975. Principles for evaluating chemicals in the environment. Washington, DC: National Academy of Sciences.

National Academy of Sciences. (Undated). Animal Models for Biomedical Research, I, II, III, IV. Washington, DC: National Academy of Sciences.

Organization for Economic Cooperation and Development (OECD). 1979. OECD short term and long term toxicology groups. (Final Report). December 31.

Padget GE. 1979. Mutagenesis in sub-mammalian systems. University Park Press. Baltimore, MD.

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peto J, Richards S, Wahrendorf J. 1980. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals in Humans, Supplement 2, Long-term and short-term screening assays for carcinogens; a critical appraisal. Lyon, France: International Agency for Research on Cancer.

Public Health Service, U.S. DHEW. 1980. National toxicology program, review of current DHEW research related to toxicology, fiscal year 1980. Washington, DC: U.S. Government Printing Office.

Public Health Service, U.S. DHEW. 1979. National toxicology program, fiscal year 1980 annual plan. Washington, DC: U.S. Government Printing Office. Publication NTP-79-7.

Public Health Service. U.S. DHEW. 1978. National toxicology program, fiscal year 1979 annual plan. Washington, DC: U.S. Government Printing Office.

Purchase IFH, et al. 1978. An evaluation of six short-term tests for detecting organic chemical carcinogenesis. Brit. J. Cancer. 37:873.

Rall DP, Chmn. 1977. Report of the subcommittee on inhalation toxicology of the DHEW Committee to coordinate toxicology and related programs III. Journ. of Env. Path. and Tox. 1:353-381.

Ramsey JC, Park CN, Ott M, Gehring PJ. 1979. Carcinogenic risk assessment: Ethylene dibromide. Toxicol. Appl. Pharmacol. 47:411-414.

Reeves AL, ed. 1981. Toxicology: Principles and practice, Vol. 1. John Wiley & Sons, New York, NY.

Riukus SJ, Legator MS. 1978. The need for combined in vitro and in vivo systems in mutagenicity screening: An analysis of 477 presumable carcinogens. USEPA Grant No. RB 04621020.

Rothman KJA. (undated). Induction and latent period. (Manuscript) Department of Epidemiology. Harvard University School of Public Health. Boston, MA.

Sega GA, Cumming RB. 1975. Ethylation pattern in mouse sperm as a function of developmental stage and time after exposure to ethyl methanesulfonate. Mutation Res. 26:448-449.

Sega GA, Cumming RB, Walton MF. 1974. Dosimetry studies on the ethylation of mouse sperm DNA after in vivo exposure to (^{3}H)ethyl methanesulfonate. Mutation Res. 24:317-333.

Spann ML, Chu KC, Wipke WT, Ouchi G. 1978. Use of computerized methods to predict metabolic pathways and metabolites. J. Environ. Path. and Toxicol. 2:123-131.

Spencer PS, Schaumburg HH. 1980. Experimental and clinical neurotoxicology. Baltimore, MD: Williams and Wilkins Co. (Chapters 7, 48-56, 60).

Staffa and Mehlman, eds. 1979. Innovations in cancer risk assessment (ED_{01} study). Park Forest South, IL: Pathotox Publishers, Inc.

Testing Standards & Guidelines Work Group, Interagency Regulatory Liaison Group. August, 1979. Draft I.R.L.G. Guidelines for Selected Acute Toxicity Tests. (see also in this report, pages 138-141, IV: Suggested Reading)

Truhaut R. 1977. Toxicology: Objectives, principles and perspectives. Ecotoxicology and Env. Safety. 1:151-173.

Van Duuren BL. 1980a. Carcinogenicity and metabolism of some halogenated olefinic and aliphatic hydrocarbons. Banbury Report 5 Ethylene Dichloride: A Potential Health Risk? Cold Spring Harbor Laboratory. pp. 189.

Van Duuren BL. 1980b. Prediction of carcinogenicity based on structure, chemical reactivity and possible metabolic pathways. J. Environ. Path. and Toxicol. 3:11-43.

Van Duuren BL. 1977. Chemical structure, reactivity, and carcinogenicity of halohydrocarbons. Environ. Health Perspect. 21:17-23.

Van Duuren BL, Melchionne S. 1980. Cofactors in environmental health and disease: Carcinogens and tumor promoters. Chapter 17 in: Environmental Health Chemistry. The Chemistry of Environmental Agents of Potential Human Hazards. J.D. McKinney, ed. Ann Arbor, MI: Ann Arbor Science Publishers, Inc. pp. 337.

Van Ryzin J. 1980. Quantitative risk assessment. J. Occupational Med. 22:321-326.

Van Ryzin J, Kamta R. 1980. The use of quantal response data to make predictions. In: The Scientific Basis of Toxicity Assessment. H. Witschi (ed.). Amsterdam: Elsevier/North-Holland Biomedical Press. pp. 273-290.

APPENDIX 1

IDENTIFICATION OF COMPUTER DATA BASES

Data Base	Complete Title	Organization Providing Service
CSIN	Chemical Substances Information Network	U.S. Environmental Protection Agency Dr. Sid Siegel (TS-777) 401 M Street, SW Washington, DC 20460
EMIC	Environmental Mutagen Information Center	Oak Ridge National Laboratory Oak Ridge, TN 37830 (TOXLINE Subfile)
PROPHET	Prophet	Bolt Beranek and Newman, Inc. Mr. David M. Fram 50 Moulton Street Cambridge, MA 02138
QUASAR	Quantitative Analytical Structure Activity Relationships	Bolt Beranek and Newman, Inc. Mr. David M. Fram 50 Moulton Street Cambridge, MA 02138 (PROPHET Subfile)
TOXLINE	Toxicology on Line	National Library of Medicine MEDLARS Management Section 8600 Rockville Pike Bethesda, MD 20209

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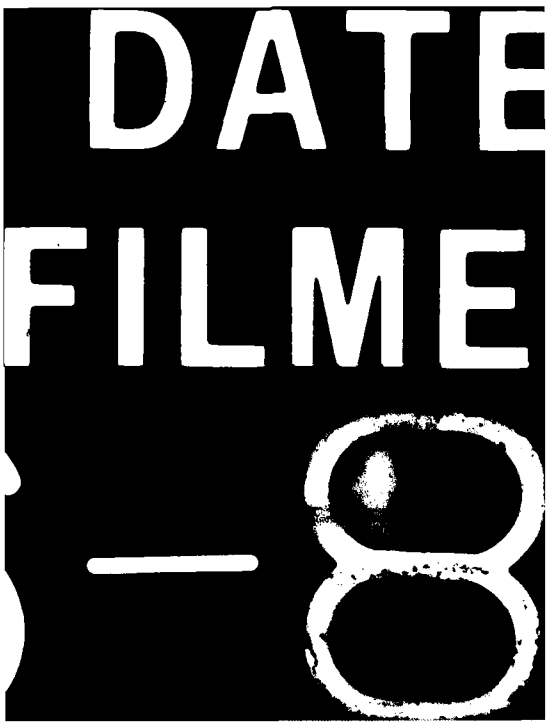
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